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(57) Abstract <p>The invention provides isolated nucleic acids molecules, designated PCIP nucleic acid molecules, which encode proteins that bind potassium channels and modulate potassium channel mediated activities. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing PCIP nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a PCIP gene has been introduced or disrupted. The invention still further provides isolated PCIP proteins, fusion proteins, antigenic peptides and anti-PCIP antibodies. Diagnostic methods utilizing compositions of the invention are also provided.</p>																																																																						

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POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR

Background of the Invention

Mammalian cell membranes are important to the structural integrity and activity
5 of many cells and tissues. Of particular interest in membrane physiology is the study of
trans-membrane ion channels which act to directly control a variety of pharmacological,
physiological, and cellular processes. Numerous ion channels have been identified
including calcium, sodium, and potassium channels, each of which have been
investigated to determine their roles in vertebrate and insect cells.

10 Because of their involvement in maintaining normal cellular homeostasis, much
attention has been given to potassium channels. A number of these potassium channels
open in response to changes in the cell membrane potential. Many voltage-gated
potassium channels have been identified and characterized by their electrophysiological
and pharmacological properties. Potassium currents are more diverse than sodium or
15 calcium currents and are further involved in determining the response of a cell to
external stimuli. The diversity of potassium channels and their important physiological
role highlights their potential as targets for developing therapeutic agents for various
diseases.

One of the best characterized classes of potassium channels are the voltage-gated
20 potassium channels. The prototypical member of this class is the protein encoded by the
Shaker gene in *Drosophila melanogaster*. Proteins of the Shal or Kv4 family are a type
of voltage-gated potassium channels that underlies many of the native A type currents
that have been recorded from different primary cells. Kv4 channels have a major role in
the repolarization of cardiac action potentials. In neurons, Kv4 channels and the A
25 currents they may comprise play an important role in modulation of firing rate, action
potential initiation and in controlling dendritic responses to synaptic inputs.

The fundamental function of a neuron is to receive, conduct, and transmit
signals. Despite the varied purpose of the signals carried by different classes of neurons,
the form of the signal is always the same and consists of changes in the electrical
30 potential across the plasma membrane of the neuron. The plasma membrane of a neuron
contains voltage-gated cation channels, which are responsible for propagating this

electrical potential (also referred to as an action potential or nerve impulse) across and along the plasma membrane.

The Kv family of channels includes, among others: (1) the delayed-rectifier potassium channels, which repolarize the membrane after each action potential to
5 prepare the cell to fire again; and (2) the rapidly inactivating (A-type) potassium channels, which are active predominantly at subthreshold voltages and and act to reduce the rate at which excitable cells reach firing threshold. In addition to being critical for action potential conduction, Kv channels also control the response to depolarizing, *e.g.*, synaptic, inputs and play a role in neurotransmitter release. As a result of these
10 activities, voltage-gated potassium channels are key regulators of neuronal excitability (Hille B., *Ionic Channels of Excitable Membranes*, Second Edition, Sunderland, MA: Sinauer, (1992)).

There is tremendous structural and functional diversity within the Kv potassium channel superfamily. This diversity is generated both by the existence of multiple genes
15 and by alternative splicing of RNA transcripts produced from the same gene. Nonetheless, the amino acid sequences of the known Kv potassium channels show high similarity. All appear to be comprised of four, pore forming α -subunits and some are known to have four cytoplasmic (β -subunit) polypeptides (Jan L.Y. *et al.* (1990) *Trends Neurosci* 13:415-419, and Pongs, O. *et al.* (1995) *Sem Neurosci.* 7:137-146). The
20 known Kv channel (α -subunits fall into four sub-families named for their homology to channels first isolated from *Drosophila*: the Kv1, or *Shaker*-related subfamily; the Kv2, or *Shab*-related subfamily; the Kv3, or *Shaw*-related subfamily; and the Kv4, or *Shal*-related subfamily.

Kv4.2 and Kv4.3 are examples of Kv channel (α -subunits of the *Shal*-related
25 subfamily. Kv4.3 has a unique neuroanatomical distribution in that its mRNA is highly expressed in brainstem monoaminergic and forebrain cholinergic neurons, where it is involved in the release of the neurotransmitters dopamine, norepinephrine, serotonin, and acetylcholine.

This channel is also highly expressed in cortical pyramidal cells and in interneurons. (Serdio P. *et al.* (1996) *J. Neurophys* 75:2174-2179). Interestingly, the Kv4.3 polypeptide is highly expressed in neurons which express the corresponding mRNA. The Kv4.3 polypeptide is expressed in the somatodendritic membranes of these
 5 cells, where it is thought to contribute to the rapidly inactivating K⁺ conductance. Kv4.2 mRNA is widely expressed in brain, and the corresponding polypeptide also appears to be concentrated in somatodendritic membranes where it also contributes to the rapidly inactivating K⁺ conductance (Sheng *et al.* (1992) *Neuron* 9:271-84). These somatodendritic A-type Kv channels, like Kv4.2 and Kv4.3, are likely involved in
 10 processes which underlie learning and memory, such as integration of sub-threshold synaptic responses and the conductance of back-propagating action potentials (Hoffman D.A. *et al.* (1997) *Nature* 387:869-875).

Thus, proteins which interact with and modulate the activity of potassium channel proteins *e.g.*, potassium channels having a Kv4.2 or Kv4.3 subunit, provide
 15 novel molecular targets to modulate neuronal or cardiac excitability, *e.g.*, action potential conduction, somatodendritic excitability and neurotransmitter release, in cells expressing these channels. In addition, detection of genetic lesions in the gene encoding these proteins could be used to diagnose and treat central nervous system disorders such as epilepsy, spinocerebellar ataxia, anxiety, depression, age-related memory loss,
 20 migraine, obesity, Parkinsons disease or Alzheimer's disease; or cardiovascular disorders such as heart failure, hypertension, atrial fibrillation, dilated cardiomyopathy, idiopathic cardiomyopathy, or angina.

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Summary of the Invention

The present invention is based, at least in part, on the discovery of novel nucleic
 20 acid molecules which encode gene products that interact with potassium channel
 proteins or possess substantial homology to the gene products of the invention that
 interact with potassium channel proteins (paralogs). Potassium channel proteins are, for
 example, potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid
 molecules of the invention and their gene products are referred to herein as "Potassium
 25 Channel Interacting Proteins", "PCIP", or "KChIP" nucleic acid and protein molecules.
 The PCIP proteins of the present invention interact with, *e.g.*, bind to a potassium
 channel protein, modulate the activity of a potassium channel protein, and/or modulate a
 potassium channel mediated activity in a cell, *e.g.*, a neuronal or cardiac cell. The PCIP
 molecules of the present invention are useful as modulating agents to regulate a variety
 30 of cellular processes, *e.g.*, neuronal or cardiac cell processes. Accordingly, in one
 aspect, this invention provides isolated nucleic acid molecules encoding PCIP proteins

aspect, this invention provides isolated nucleic acid molecules encoding PCIP proteins or biologically active portions thereof, as well as nucleic acid fragments suitable as primers or hybridization probes for the detection of PCIP-encoding nucleic acids.

In one embodiment, a PCIP nucleic acid molecule of the invention is at least
5 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to the nucleotide sequence (*e.g.*, to the entire length of the nucleotide sequence) shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID
10 NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947,
15 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a complement thereof.

In another preferred embodiment, the isolated nucleic acid molecule includes the nucleotide sequence shown SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID
20 NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or a complement thereof. In another preferred embodiment, the nucleic acid molecule includes a fragment of at least 300, 350, 400, 426, 471, or 583 nucleotides of
25 the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
30 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or a complement thereof.

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In another embodiment, a PCIP nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence sufficiently identical to the amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In a preferred embodiment, a PCIP nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to the amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994.

In another preferred embodiment, an isolated nucleic acid molecule encodes the amino acid sequence of 1v, 9q, p19, W28559, KChIP4a, KChIP4b, 33b07, 1p, and rat 7s protein. In yet another preferred embodiment, the nucleic acid molecule includes a nucleotide sequence encoding a protein having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID

NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In yet another preferred embodiment, the nucleic acid molecule is at least 426, 471, or 583 nucleotides in length and encodes a protein having a PCIP activity (as described herein).

Another embodiment of the invention features nucleic acid molecules, preferably PCIP nucleic acid molecules, which specifically detect PCIP nucleic acid molecules relative to nucleic acid molecules encoding non-PCIP proteins. For example, in one embodiment, such a nucleic acid molecule is at least 426, 400-450, 471, 450-500, 500-550, 583, 550-600, 600-650, 650-700, 700-750, 750-800 or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a complement thereof. In preferred embodiments, the nucleic acid molecules are at least 15 (*e.g.*, contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 93-126, 360-462, 732-825, 1028-1054, or 1517-1534 of SEQ ID NO:7. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 93-126, 360-462, 732-825, 1028-1054, or 1517-1534 of SEQ ID NO:7.

In other preferred embodiments, the nucleic acid molecules are at least 15 (*e.g.*, contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 1-14, 49-116, 137-311, 345-410, 430-482, 503-518, 662-693, 1406-1421, 1441-1457, 1478-1494, or 1882-1959 of SEQ ID NO:13. In other preferred embodiments, the

nucleic acid molecules comprise nucleotides 1-14, 49-116, 137-311, 345-410, 430-482, 503-518, 662-693, 1406-1421, 1441-1457, 1478-1494, or 1882-1959 of SEQ ID NO:13.

In preferred embodiments, the nucleic acid molecules are at least 15 (*e.g.*, contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides
 5 932-1527, 1548-1765, 1786-1871, 1908-2091, 2259-2265, or 2630-2654 of SEQ ID NO:35. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 932-1527, 1548-1765, 1786-1871, 1908-2091, 2259-2265, or 2630-2654 of SEQ ID NO:35.

In other preferred embodiments, the nucleic acid molecule encodes a naturally
 10 occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID
 15 NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, wherein the nucleic acid molecule hybridizes to a
 20 nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
 25 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 under stringent conditions.

Another embodiment of the invention provides an isolated nucleic acid molecule which is antisense to a PCIP nucleic acid molecule, *e.g.*, the coding strand of a PCIP nucleic acid molecule.

Another aspect of the invention provides a vector comprising a PCIP nucleic acid molecule. In certain embodiments, the vector is a recombinant expression vector. In another embodiment, the invention provides a host cell containing a vector of the invention. The invention also provides a method for producing a protein, preferably a
5 PCIP protein, by culturing in a suitable medium, a host cell, *e.g.*, a mammalian host cell such as a non-human mammalian cell, of the invention containing a recombinant expression vector, such that the protein is produced.

Another aspect of this invention features isolated or recombinant PCIP proteins and polypeptides. In one embodiment, the isolated protein, preferably a PCIP protein,
10 includes at least one calcium binding domain. In a preferred embodiment, the protein, preferably a PCIP protein, includes at least one calcium binding domain and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID
15 NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited
20 with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another preferred embodiment, the protein, preferably a PCIP protein, includes at least one calcium binding domain and modulates a potassium channel mediated activity. In yet another preferred embodiment, the protein, preferably a PCIP
25 protein, includes at least one calcium binding domain and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ
30 ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID

NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71.

In another embodiment, the invention features fragments of the proteins having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, wherein the fragment comprises at least 15 amino acids (*e.g.*, contiguous amino acids) of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another embodiment, the protein, preferably a PCIP protein, has the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

In another embodiment, the invention features an isolated protein, preferably a PCIP protein, which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ

ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or a complement thereof.

The proteins of the present invention or biologically active portions thereof, can be operatively linked to a non-PCIP polypeptide (*e.g.*, heterologous amino acid sequences) to form fusion proteins. The invention further features antibodies, such as monoclonal or polyclonal antibodies, that specifically bind proteins of the invention, preferably PCIP proteins. In addition, the PCIP proteins or biologically active portions thereof can be incorporated into pharmaceutical compositions, which optionally include pharmaceutically acceptable carriers.

In another aspect, the present invention provides a method for detecting the presence of a PCIP nucleic acid molecule, protein or polypeptide in a biological sample by contacting the biological sample with an agent capable of detecting a PCIP nucleic acid molecule, protein or polypeptide such that the presence of a PCIP nucleic acid molecule, protein or polypeptide is detected in the biological sample.

In another aspect, the present invention provides a method for detecting the presence of PCIP activity in a biological sample by contacting the biological sample with an agent capable of detecting an indicator of PCIP activity such that the presence of PCIP activity is detected in the biological sample.

In another aspect, the invention provides a method for modulating PCIP activity comprising contacting a cell capable of expressing PCIP with an agent that modulates PCIP activity such that PCIP activity in the cell is modulated. In one embodiment, the agent inhibits PCIP activity. In another embodiment, the agent stimulates PCIP activity. In one embodiment, the agent is an antibody that specifically binds to a PCIP protein. In another embodiment, the agent modulates expression of PCIP by modulating transcription of a PCIP gene or translation of a PCIP mRNA. In yet another embodiment, the agent is a nucleic acid molecule having a nucleotide sequence that is antisense to the coding strand of a PCIP mRNA or a PCIP gene.

In one embodiment, the methods of the present invention are used to treat a subject having a disorder characterized by aberrant PCIP protein or nucleic acid expression or activity by administering an agent which is a PCIP modulator to the subject. In one embodiment, the PCIP modulator is a PCIP protein. In another
5 embodiment the PCIP modulator is a PCIP nucleic acid molecule. In yet another embodiment, the PCIP modulator is a peptide, peptidomimetic, or other small molecule. In a preferred embodiment, the disorder characterized by aberrant PCIP protein or nucleic acid expression is a CNS disorder or a cardiovascular disorder.

The present invention also provides a diagnostic assay for identifying the
10 presence or absence of a genetic alteration characterized by at least one of (i) aberrant modification or mutation of a gene encoding a PCIP protein; (ii) mis-regulation of the gene; and (iii) aberrant post-translational modification of a PCIP protein, wherein a wild-type form of the gene encodes a protein with a PCIP activity.

In another aspect the invention provides a method for identifying a compound
15 that binds to or modulates the activity of a PCIP protein, by providing an indicator composition comprising a PCIP protein having PCIP activity, contacting the indicator composition with a test compound, and determining the effect of the test compound on PCIP activity in the indicator composition to identify a compound that modulates the activity of a PCIP protein.

20

Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description of the Drawings

25 *Figure 1* depicts the cDNA sequence and predicted amino acid sequence of human 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1463 of SEQ ID NO:1. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:2.

Figure 2 depicts the cDNA sequence and predicted amino acid sequence of rat 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1856 of SEQ ID NO:3.
30 The amino acid sequence corresponds to amino acids 1 to 245 of SEQ ID NO:4.

Figure 3 depicts the cDNA sequence and predicted amino acid sequence of mouse 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1907 of SEQ ID NO:5. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:6.

Figure 4 depicts the cDNA sequence and predicted amino acid sequence of rat 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1534 of SEQ ID NO:7. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:8.

Figure 5 depicts the cDNA sequence and predicted amino acid sequence of mouse 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1540 of SEQ ID NO:9. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:10.

Figure 6 depicts the cDNA sequence and predicted amino acid sequence of rat 1vn. The nucleotide sequence corresponds to nucleic acids 1 to 955 of SEQ ID NO:11. The amino acid sequence corresponds to amino acids 1 to 203 of SEQ ID NO:12.

Figure 7 depicts the cDNA sequence and predicted amino acid sequence of human 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2009 of SEQ ID NO:13. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:14.

Figure 8 depicts the cDNA sequence and predicted amino acid sequence of rat 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 1247 of SEQ ID NO:15. The amino acid sequence corresponds to amino acids 1 to 257 of SEQ ID NO:16.

Figure 9 depicts the cDNA sequence and predicted amino acid sequence of mouse 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2343 of SEQ ID NO:17. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:18.

Figure 10 depicts the cDNA sequence and predicted amino acid sequence of human 9qm. The nucleotide sequence corresponds to nucleic acids 1 to 1955 of SEQ ID NO:19. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:20.

Figure 11 depicts the cDNA sequence and predicted amino acid sequence of rat 9qm. The nucleotide sequence corresponds to nucleic acids 1 to 2300 of SEQ ID NO:21. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:22.

Figure 12 depicts the cDNA sequence and predicted amino acid sequence of human 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 1859 of SEQ ID NO:23. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID NO:24.

5 *Figure 13* depicts the cDNA sequence and predicted amino acid sequence of monkey 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 2191 of SEQ ID NO:25. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID NO:26.

10 *Figure 14* depicts the cDNA sequence and predicted amino acid sequence of rat 9qc. The nucleotide sequence corresponds to nucleic acids 1 to 2057 of SEQ ID NO:27. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:28.

Figure 15 depicts the cDNA sequence and predicted amino acid sequence of rat 8t. The nucleotide sequence corresponds to nucleic acids 1 to 1904 of SEQ ID NO:29. The amino acid sequence corresponds to amino acids 1 to 225 of SEQ ID NO:30.

15 *Figure 16* depicts the cDNA sequence and predicted amino acid sequence of human p19. The nucleotide sequence corresponds to nucleic acids 1 to 619 of SEQ ID NO:31. The amino acid sequence corresponds to amino acids 1 to 200 of SEQ ID NO:32.

20 *Figure 17* depicts the cDNA sequence and predicted amino acid sequence of rat p19. The nucleotide sequence corresponds to nucleic acids 1 to 442 of SEQ ID NO:33. The amino acid sequence corresponds to amino acids 1 to 109 of SEQ ID NO:34.

25 *Figure 18* depicts the cDNA sequence and predicted amino acid sequence of mouse p19. The nucleotide sequence corresponds to nucleic acids 1 to 2644 of SEQ ID NO:35. The amino acid sequence corresponds to amino acids 1 to 256 of SEQ ID NO:36.

Figure 19 depicts the cDNA sequence and predicted amino acid sequence of human W28559. The nucleotide sequence corresponds to nucleic acids 1 to 380 of SEQ ID NO:37. The amino acid sequence corresponds to amino acids 1 to 126 of SEQ ID NO:38.

Figure 20 depicts the cDNA sequence and predicted amino acid sequence of human P193. The nucleotide sequence corresponds to nucleic acids 1 to 2176 of SEQ ID NO:39. The amino acid sequence corresponds to amino acids 1 to 41 of SEQ ID NO:40.

5 *Figure 21* depicts a schematic representation of the rat 1v, the rat 9qm, and the mouse P19 proteins, aligned to indicate the conserved domains among these proteins.

Figure 22 depicts the genomic DNA sequence of human 9q. *Figure 22A* depicts exon 1 and its flanking intron sequences (SEQ ID NO:46). *Figure 22B* depicts exons 2-11 and the flanking intron sequences (SEQ ID NO:47).

10 *Figure 23* depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4a. The nucleotide sequence corresponds to nucleic acids 1 to 2413 of SEQ ID NO:48. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:49.

15 *Figure 24* depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4b. The nucleotide sequence corresponds to nucleic acids 1 to 1591 of SEQ ID NO:50. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:51.

20 *Figure 25* depicts an alignment of KChIP4a, KChIP4b, 9ql, 1v, p19, and related human paralog (hsncspara) W28559. Amino acids identical to the consensus are shaded in black, conserved amino acids are shaded in gray.

Figure 26 depicts the cDNA sequence and predicted amino acid sequence of rat 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 2051 of SEQ ID NO:52. The amino acid sequence corresponds to amino acids 1 to 407 of SEQ ID NO:53.

25 *Figure 27* depicts the cDNA sequence and predicted amino acid sequence of human 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 4148 of SEQ ID NO:54. The amino acid sequence corresponds to amino acids 1 to 414 of SEQ ID NO:55.

30 *Figure 28* depicts the cDNA sequence and predicted amino acid sequence of rat 1p. The nucleotide sequence corresponds to nucleic acids 1 to 2643 of SEQ ID NO:56. The amino acid sequence corresponds to amino acids 1 to 267 of SEQ ID NO:57.

Figure 29 depicts the cDNA sequence and predicted amino acid sequence of rat 7s. The nucleotide sequence corresponds to nucleic acids 1 to 2929 of SEQ ID NO:58. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:59.

Figure 30 depicts the cDNA sequence and predicted amino acid sequence of rat 29x. The nucleotide sequence corresponds to nucleic acids 1 to 1489 of SEQ ID NO:60. The amino acid sequence corresponds to amino acids 1 to 351 of SEQ ID NO:61.

Figure 31 depicts the cDNA sequence of rat 25r. The nucleotide sequence corresponds to nucleic acids 1 to 1194 of SEQ ID NO:62.

Figure 32 depicts the cDNA sequence and predicted amino acid sequence of rat 5p. The nucleotide sequence corresponds to nucleic acids 1 to 600 of SEQ ID NO:63. The amino acid sequence corresponds to amino acids 1 to 95 of SEQ ID NO:64.

Figure 33 depicts the cDNA sequence and predicted amino acid sequence of rat 7q. The nucleotide sequence corresponds to nucleic acids 1 to 639 of SEQ ID NO:65. The amino acid sequence corresponds to amino acids 1 to 212 of SEQ ID NO:66.

Figure 34 depicts the cDNA sequence and predicted amino acid sequence of rat 19r. The nucleotide sequence corresponds to nucleic acids 1 to 816 of SEQ ID NO:67. The amino acid sequence corresponds to amino acids 1 to 271 of SEQ ID NO:68.

Figure 35 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4c. The nucleotide sequence corresponds to nucleic acids 1 to 2263 of SEQ ID NO:69. The amino acid sequence corresponds to amino acids 1 to 229 of SEQ ID NO:70.

Figure 36 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4d. The nucleotide sequence corresponds to nucleic acids 1 to 2259 of SEQ ID NO:71. The amino acid sequence corresponds to amino acids 1 to 250 of SEQ ID NO:72.

Figure 37 depicts an alignment of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Figure 38 depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP2 (9ql). Cells are voltage clamped at -80 mV and stepped from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 38* further depicts a table showing the amplitude and kinetic effects of KChIP2 (9ql) on Kv4.2. KChIP2 expression alters the

peak current amplitude, inactivation and recovery from inactivation time constants, and activation $V_{1,2}$.

Figure 39 depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP3 (p19). Cells are voltage clamped at -80 mV and stepped from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 39* further depicts a table showing the amplitude and kinetic effects of KChIP3 (p19) on Kv4.2. KChIP3 causes alterations in peak current and inactivation and recovery from inactivation time constants.

Figure 40 depicts results from electrophysiological experiments demonstrating that coexpression of KChIP1 dramatically alters the current density and kinetics of Kv4.2 channels expressed in CHO cells.

Figure 40A depicts current traces from a Kv4.2 transfected CHO cell. Current was evoked by depolarizing the cell sequentially from a holding potential of -80 mV to test potentials from -60 to 50 mV. Current traces are leak subtracted using a p/5 protocol. The current axis is shown at the same magnification as in (b) to emphasize the change in current amplitudes. Inset- Single current trace at 50mV at an expanded current axis to show the kinetics of current activation and inactivation.

Figure 40B depicts current traces as in (a), but from a cell transfected with equal amounts of DNA for Kv4.2 and KChIP1.

Figure 40C depicts peak current amplitude at all voltages from cells transfected with Kv4.2 alone (n=11) or cotransfected with KChIP1 (n=9).

Figures 40D and 40E depict recovery from inactivation using a two pulse protocol. Kv4.2 alone (D) or coexpressed with KChIP1 (E) is driven into the inactivated state using a first pulse to 50 mV, then a second pulse to 50 mV is applied at varying times after the first pulse. Holding potential is -80 mV before and after all pulses.

Figure 40F depicts a summary of the percentage the peak current recovers between pulses for Kv4.2 (n=8) and Kv4.2 plus KChIP1 (n=5) transfected cells. The time constant of recovery from inactivation is fit to a single exponential.

Figure 41 depicts an alignment of human KChIP family members with closely related members of the recoverin family of Ca²⁺ sensing proteins. (HIP:human hippocalcin; NCS1:rat neuronal calcium sensor 1). The alignment was performed using

the MegAlign program for Macintosh (version 4.00 from DNASTAR) using the Clustal method with the PAM250 residue weight table and default parameters, and shaded using BOXSHADES. Residues identical to the consensus are shaded black, conservative substitutions are shaded grey. X, Y, Z and -X, -Y, -Z denote the positions of residues
5 which are responsible for binding to the calcium ion in the EF hand.

Figure 42 depicts a physical map of the IOSCA region.

Figure 43 depicts a linkage map showing the location of h9q and known markers associating with IOSCA and epilepsy.

10 **Detailed Description of the Invention**

The present invention is based, at least in part, on the discovery of novel nucleic acid molecules which encode gene products that interact with potassium channel proteins or possess substantial homology to the gene products of the invention that interact with potassium channel proteins (paralogs). Potassium channel proteins are, for
15 example, potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid molecules of the invention and their gene products are referred to herein as "Potassium Channel Interacting Proteins", "PCIP", or "KChIP" nucleic acid and protein molecules. Preferably, the PCIP proteins of the present invention interact with, *e.g.*, bind to a potassium channel protein, modulate the activity of a potassium channel protein, and/or
20 modulate a potassium channel mediated activity in a cell, *e.g.*, a neuronal or cardiac cell.

As used herein, the term "PCIP family" when referring to the protein and nucleic acid molecules of the invention is intended to mean two or more proteins or nucleic acid molecules having a PCIP activity as defined herein. Such PCIP family members can be naturally or non-naturally occurring and can be from either the same or different species.
25 For example, a PCIP family can contain a first protein of human origin, as well as other, distinct proteins of human origin or alternatively, can contain homologues of non-human origin.

As used interchangeably herein, a "PCIP activity", "biological activity of PCIP" or "functional activity of PCIP", refers to an activity exerted by a PCIP protein,
30 polypeptide or nucleic acid molecule on a PCIP responsive cell or on a PCIP protein substrate, as determined *in vivo*, or *in vitro*, according to standard techniques. In one

embodiment, a PCIP activity is a direct activity, such as an association with a PCIP-target molecule. As used herein, a "target molecule" or "binding partner" is a molecule with which a PCIP protein binds or interacts in nature, such that PCIP-mediated function is achieved. A PCIP target molecule can be a non-PCIP molecule or a PCIP protein or polypeptide of the present invention. In an exemplary embodiment, a PCIP target molecule is a PCIP ligand. Alternatively, a PCIP activity is an indirect activity, such as a cellular signaling activity mediated by interaction of the PCIP protein with a PCIP ligand. The biological activities of PCIP are described herein.

For example, the PCIP proteins of the present invention can have one or more of the following activities: (1) they can interact with (*e.g.*, bind to) a potassium channel protein or portion thereof; (2) they can regulate the phosphorylation state of a potassium channel protein or portion thereof; (3) they can associate with (*e.g.*, bind) calcium and can, for example, act as calcium dependent kinases, *e.g.*, phosphorylate a potassium channel or a G-protein coupled receptor in a calcium-dependent manner; (4) they can associate with (*e.g.*, bind) calcium and can, for example, act in a calcium-dependent manner in cellular processes, *e.g.*, act as calcium dependent transcription factors; (5) they can modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal cell such as a sensory neuron cell or a motor neuron cell, or a cardiac cell) to, for example, beneficially affect the cell; (6) they can modulate chromatin formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) they can modulate vesicular traffic and protein transport in a cell, *e.g.*, a neuronal or cardiac cell; (8) they can modulate cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell; (9) they can regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) they can modulate cellular proliferation; (11) they can modulate the release of neurotransmitters; (12) they can modulate membrane excitability; (13) they can influence the resting potential of membranes; (14) they can modulate wave forms and frequencies of action potentials; and (15) they can modulate thresholds of excitation.

As used herein, a "potassium channel" includes a protein or polypeptide that is involved in receiving, conducting, and transmitting signals in an excitable cell. Potassium channels are typically expressed in electrically excitable cells, *e.g.*, neurons, cardiac, skeletal and smooth muscle, renal, endocrine, and egg cells, and can form

heteromultimeric structures, *e.g.*, composed of pore-forming and cytoplasmic subunits. Examples of potassium channels include: (1) the voltage-gated potassium channels, (2) the ligand-gated potassium channels, and (3) the mechanically-gated potassium channels. For a detailed description of potassium channels, see Kandel E.R. *et al.*,
5 Principles of Neural Science, second edition, (Elsevier Science Publishing Co., Inc., N.Y. (1985)), the contents of which are incorporated herein by reference. The PCIP proteins of the present invention have been shown to interact with, for example, potassium channels having a Kv4.3 subunit or a Kv4.2 subunit.

As used herein, a "potassium channel mediated activity" includes an activity
10 which involves a potassium channel, *e.g.*, a potassium channel in a neuronal cell or a cardiac cell, associated with receiving, conducting, and transmitting signals in, for example, the nervous system or in the heart. Potassium channel mediated activities include release of neurotransmitters, *e.g.*, dopamine or norepinephrine, from cells, *e.g.*, neuronal or cardiac cells; modulation of resting potential of membranes, wave forms and
15 frequencies of action potentials, and thresholds of excitation; and modulation of processes such as integration of sub-threshold synaptic responses and the conductance of back-propagating action potentials in, for example, neuronal cells or cardiac cells.

As the PCIP proteins of the present invention modulate potassium channel mediated activities, they may be useful as novel diagnostic and therapeutic agents for
20 potassium channel associated disorders and/or nervous system related disorders. Moreover, the PCIP proteins of the present invention modulate Kv4 potassium channels, *e.g.*, potassium channels having a Kv4.2 or Kv4.3 subunit, which underlie the voltage-gated K⁺ current known as I_{to} (transient outward current) in the mammalian heart (Kaab S. *et al.* (1998) *Circulation* 98(14):1383-93; Dixon J.E. *et al.* (1996) *Circulation*
25 *Research* 79(4):659-68; Nerbonne JM (1998) *Journal of Neurobiology* 37(1):37-59; Barry D.M. *et al.* (1998) *Circulation Research* 83(5):560-7; Barry D.M. *et al.* (1996) *Annual Review of Physiology* 58:363-94. This current underlies the rapid repolarization of cardiac myocytes during an action potential. It also participates in the inter-beat interval by controlling the rate at which cardiac myocytes reach the threshold for firing a
30 subsequent action potential.

This current is also known to be down regulated in patients with cardiac hypertrophy, resulting in prolongation of the cardiac action potential. In these patients, action potential prolongation is thought to produce changes in calcium load and calcium handling within the myocardium, which contributes to the progression of cardiac disease from hypertrophy to heart failure (Wickenden *et al.* (1998) *Cardiovascular Research* 37:312). Interestingly, several PCIPs of the present invention (*e.g.*, 9ql, 9qm, 9qs, shown in SEQ ID NOs:13, 15, 17, 19, 21, 23, and 25) bind to and modulate potassium channels containing a Kv4.2 or Kv4.3 subunit and contain calcium binding EF-hand domains. Because of mutations in these PCIP genes, defects in the expression of these calcium-binding PCIP proteins themselves, or defects in the interaction between these PCIPs and Kv4.2 or Kv4.3 channels, might be expected to lead to decreases in KV4.3 or Kv4.3(I_m) currents in the myocardium, therapeutic agents that alter PCIP expression or modulate the interaction between these PCIPs and Kv4.2 or Kv4.3 may be extremely valuable agents to slow or prevent the progression of disease from hypertrophy to heart failure.

As used herein, a "potassium channel associated disorder" includes a disorder, disease or condition which is characterized by a misregulation of a potassium channel mediated activity. Potassium channel associated disorders can detrimentally affect conveyance of sensory impulses from the periphery to the brain and/or conductance of motor impulses from the brain to the periphery; integration of reflexes; interpretation of sensory impulses; and emotional, intellectual (*e.g.*, learning and memory), or motor processes. Potassium channel associated disorders can further detrimentally affect electrical impulses that stimulate the cardiac muscle fibers to contract. Examples of potassium channel associated disorders include nervous system related disorders, as well as cardiovascular disorders.

As used herein, a "nervous system related disorder" includes a disorder, disease or condition which affects the nervous system. Examples of potassium channel associated disorders and nervous system related disorders include cognitive disorders, *e.g.*, memory and learning disorders, such as amnesia, apraxia, agnosia, amnesic dysnomia, amnesic spatial disorientation, Kluver-Bucy syndrome, Alzheimer's related memory loss (Eglen R.M. (1996) *Pharmacol. and Toxicol.* 78(2):59-68; Perry E.K.

- (1995) *Brain and Cognition* 28(3):240-58) and learning disability: disorders affecting consciousness, *e.g.*, visual hallucinations, perceptual disturbances, or delirium associated with Lewy body dementia; schizo-affective disorders (Dean B. (1996) *Mol. Psychiatry* 1(1):54-8), schizophrenia with mood swings (Bymaster F.P. (1997) *J. Clin. Psychiatry* 58 (suppl.10):28-36; Yeomans J.S. (1995) *Neuropharmacol.* 12(1):3-16; Reimann D. (1994) *J. Psychiatric Res.* 28(3):195-210), depressive illness (primary or secondary); affective disorders (Janowsky D.S. (1994) *Am. J. Med. Genetics* 54(4):335-44); sleep disorders (Kimura F. (1997) *J. Neurophysiol.* 77(2):709-16), *e.g.*, REM sleep abnormalities in patients suffering from, for example, depression (Reimann D. (1994) *J. Psychosomatic Res.* 38 Suppl. 1:15-25; Bourgin P. (1995) *Neuroreport* 6(3): 532-6), paradoxical sleep abnormalities (Sakai K. (1997) *Eur. J. Neuroscience* 9(3):415-23), sleep-wakefulness, and body temperature or respiratory depression abnormalities during sleep (Shuman S.L. (1995) *Am. J. Physiol.* 269(2 Pt 2):R308-17; Mallick B.N. (1997) *Brain Res.* 750(1-2):311-7). Other examples of nervous system related disorders include disorders affecting pain generation mechanisms, *e.g.*, pain related to irritable bowel syndrome (Mitch C.H. (1997) *J. Med. Chem.* 40(4):538-46; Shannon H.E. (1997) *J. Pharmac. and Exp. Therapeutics* 281(2):884-94; Bouaziz H. (1995) *Anesthesia and Analgesia* 80(6):1140-4; or Guimaraes A.P. (1994) *Brain Res.* 647(2):220-30) or chest pain; movement disorders (Monassi C.R. (1997) *Physiol. and Behav.* 62(1):53-9), *e.g.*, Parkinson's disease related movement disorders (Finn M. (1997) *Pharmacol. Biochem. & Behavior* 57(1-2):243-9; Mayorga A.J. (1997) *Pharmacol. Biochem. & Behavior* 56(2):273-9); eating disorders, *e.g.*, insulin hypersecretion related obesity (Maccario M. (1997) *J. Endocrinol. Invest.* 20(1):8-12; Premawardhana L.D. (1994) *Clin. Endocrinol.* 40(5): 617-21); drinking disorders, *e.g.*, diabetic polydipsia (Murzi E. (1997) *Brain Res.* 752(1-2):184-8; Yang X. (1994) *Pharmacol. Biochem. & Behavior* 49(1):1-6); neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, epileptic syndromes, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis,

mania, anxiety disorders, bipolar affective disorders, or phobic disorders; neurological disorders, *e.g.*, migraine; spinal cord injury; stroke; and head trauma.

As used herein, "epilepsy" includes a common neurological disorder caused by disturbances in the normal electrical functions of the brain. In normal brain function
5 millions of tiny electrical charges pass from nerve cells in the brain to all parts of the body. In patients with epilepsy, this normal pattern is interrupted by sudden and unusually intense bursts of electrical energy, which may briefly affect a person's consciousness, bodily movements, or sensations. These physical changes are called epileptic seizures. There are two categories of seizures: partial seizures, which occur in
10 one area of the brain, and generalized seizures, which affect nerve cells throughout the brain. Epilepsy may result from a brain injury before, during, or after birth; head trauma; poor nutrition; some infectious diseases; brain tumors; and some poisons. However, in many cases the cause is unknown. Attacks of epilepsy may be preceded by a feeling of unease or sensory discomfort called an aura, which indicates the beginning
15 of the seizure. Signs of an impending epileptic seizure, which vary among patients, may include visual phenomena such as flickering lights or "sunbursts." Recently, a genetic linkage for epilepsy has been found on chromosome 10q, near marker D10S192: 10q22-q24 (Ottman *et al.* (1995) *Nature Genetics* 10:56-60). The many forms of epilepsy include: grand mal, Jacksonian, myoclonic progressive familial, petit mal, Lennox-Gastaut syndrome, febrile seizures, psycho-motor, and temporal lobe. The observations
20 described herein are particularly useful in developing treatments for partial epilepsy.

As used herein, "ataxia" includes a common neurological disorder caused by disturbances in the normal electrical functions of the brain. Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant disorder which is genetically linked to the short arm
25 of chromosome 6 based on linkage to the human major histocompatibility complex (HLA). See, for example, H. Yakura *et al.* (1974) *N. Engl. J. Med.*, 291, 154-155; and J. F. Jackson *et al.* (1977) *N. Engl. J. Med* 296, 1138-1141. SCA1 has been shown to be tightly linked to the marker D6S89 on the short arm of chromosome 6, telomeric to HLA. See, for example, L. P. W. Ranum *et al.*, *Am. J. Hum. Genet.*, 49, 31-41
30 (1991); and H. Y. Zoghbi *et al.*, *Am. J. Hum. Genet.*, 49, 23-30 (1991). The

observations described herein are particularly useful in developing treatments for infantile onset spinocerebellar ataxia (IOSCA).

As used herein, a "cardiovascular disorder" includes a disorder affecting the cardiovascular system, *e.g.*, the heart. Examples of cardiovascular disorders include arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia. In a preferred embodiment, the cardiovascular disorder is associated with an abnormal I_{to} current.

Some members of a PCIP family may also have common structural characteristics, such as a common structural domain or motif or a sufficient amino acid or nucleotide sequence homology as defined herein. Such PCIP family members can be naturally or non-naturally occurring and can be from either the same or different species. For example, a PCIP family can contain a first protein of human origin, as well as other, distinct proteins of human origin or alternatively, can contain homologues of non-human origin.

For example, members of a PCIP family which have common structural characteristics, may comprise at least one "calcium binding domain". As used herein, the term "calcium binding domain" includes an amino acid domain, *e.g.*, an EF hand (Baimbridge K.G. *et al.* (1992) *TINS* 15(8): 303-308), which is involved in calcium binding. Preferably, a calcium binding domain has a sequence, which is substantially identical to the consensus sequence:

EO••OO••ODKDGDG•O•••EF••OO. (SEQ ID NO:41).

O can be I, L, V or M, and "*" indicates a position with no strongly preferred residue. Each residue listed is present in more than 25% of sequences, and those underlined are present in more than 80% of sequences. Amino acid residues 126-154 and 174-202 of the human 1v protein, amino acid residues 126-154 and 174-202 of the rat 1v protein, amino acid residues 137-165 and 185-213 of the rat 1vl protein, amino acid residues 142-170 of the rat 1vn protein, amino acid residues 126-154 and 174-202 of the mouse 1v protein, amino acid residues 137-165 and 185-213 of the mouse 1vl protein, amino acid residues 144-172, 180-208, and 228-256 of the human 9q1 protein, amino acid residues 126-154, 162-190, and 210-238 of the human 9qm protein, amino acid residues 94-122, 130-158, and 178-206 of the human 9qs protein, amino acid residues 126-154, 162-190, and 210-238 of the rat 9qm protein, amino acid residues 131-159, 167-195, and 215-243 of the rat 9ql protein, amino acid residues 126-154, 162-190, and 210-238 of the rat 9qc protein, amino acid residues 99-127, 135-163, and 183-211 of the rat 8t protein, amino acid residues 144-172, 180-208, and 228-256 of the mouse 9ql protein, amino acid residues 94-122, 130-158, and 178-206 of the monkey 9qs protein, amino acid residues 94-122, 130-158, and 178-206 of the human p19 protein, amino acid residues 19-47 and 67-95 of the rat p19 protein, and amino acid residues 130-158, 166-194, and 214-242 of the mouse p19 protein comprise calcium binding domains (EF hands) (see Figure 21). Amino acid residues 116-127 and 152-163 of the monkey KChIP4a and KChIP4b proteins comprise calcium binding domains.

In another embodiment, the isolated PCIP proteins of the present invention are identified based on the presence of at least one conserved carboxyl-terminal domain which includes an amino acid sequence of about 100-200 amino acid residues in length, preferably 150-200 amino acid residues in length, and more preferably 185 amino acid residues in length, and which includes three EF hands. PCIP proteins of the present invention preferably contain a carboxyl-terminal domain which is at least about 70%, 71%, 74%, 75%, 76%, 80%, or more identical to the carboxyl terminal 185 amino acid residues of rat 1v, rat 9q, or mouse p19 (see Figures 21, 25, and 41).

Members of the PCIP family which also have common structural characteristics are listed in Table I and described below. The invention provides full length human, mouse, and rat 1v cDNA clones, full length mouse and rat cDNA clones of 1v splice

variant 1vl, a partial rat cDNA clone of 1v splice variant 1vn, and the proteins encoded by these cDNAs. The invention further provides full length human and mouse and partial rat 9ql cDNA clones, full length human and rat cDNA clones of 9ql splice variant 9qm, full length human and monkey cDNA clones of 9ql splice variant 9qs, a full length
5 rat cDNA clone of 9ql splice variant 9qc, a partial rat cDNA clone of 9ql splice variant 8t, and the proteins encoded by these cDNAs. The invention also provides full length mouse and human and partial rat p19 cDNA clones and the proteins encoded by these cDNAs. A full length human cDNA clone of p19 is provided, and a partial clone p193, representing the 3' end of the human p19 cDNA. In addition, the invention provides a
10 partial human W28559 cDNA clone and the protein encoded by this cDNA. The invention further provides a full length monkey clone, KChIP4a, and a corresponding full length splice variant, KChIP4b and the proteins encoded by these cDNAs.

Other members of the PCIP family, *e.g.*, members of the PCIP family which do not have common structural characteristics, are listed in Table II and are described
15 below. The present invention provides a full length human and a partial length rat 33b07 clone and the proteins encoded by these cDNAs. The present invention further provides partial length rat 1p clone and the protein encoded by this cDNA. In addition, the present invention provides a partial length rat 7s clone and the protein encoded by this cDNA.

20 The present invention further provides PCIP family members which represent previously identified cDNAs (29x, 25r, 5p, 7q, and 19r). These previously identified cDNAs are identified herein as PCIP family members, *i.e.*, as molecules which have a PCIP activity, as described herein. Accordingly, the present invention provides methods for using these previously identified cDNAs, *e.g.*, methods for using these cDNAs in the
25 screening assays, the diagnostic assays, the prognostic assays, and the methods of treatment described herein.

The PCIP molecules of the present invention were initially identified based on their ability, as determined using yeast two-hybrid assays (described in detail in Example 1), to interact with the amino-terminal 180 amino acids of rat Kv4.3 subunit.
30 Further binding studies with other potassium subunits were performed to demonstrate specificity of the PCIP for Kv4.3 and Kv4.2. *In situ* localization, immuno-histochemical

methods, co-immunoprecipitation and patch clamping methods were then used to clearly demonstrate that the PCIPs of the present invention interact with and modulate the activity of potassium channels, particularly those comprising a 4.3 or 4.2 subunit.

Several novel human, mouse, monkey, and rat PCIP family members have been identified, referred to herein as 1v, 9q, p19, W28559, KChIP4, 33b07, 1p, and rat 7s proteins and nucleic acid molecules. The human, rat, and mouse cDNAs encoding the 1v polypeptide are represented by SEQ ID NOs:1, 3, and 5, and shown in Figures 1, 2, and 3, respectively. In the brain, 1v mRNA is highly expressed in neocortical and hippocampal interneurons, in the thalamic reticular nucleus and medial habenula, in basal forebrain and striatal cholinergic neurons, in the superior colliculus, and in cerebellar granule cells. The 1v polypeptide is highly expressed in the somata, dendrites, axons and axon terminals of cells that express 1v mRNA. Splice variants of the 1v gene have been identified in rat and mouse and are represented by SEQ ID NOs: 7, 9, and 11 and shown in Figures 4, 5, and 6, respectively. 1v polypeptide interacts with potassium channels comprising Kv4.3 or kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot, the 1v transcripts (mRNA) are expressed predominantly in the brain

The 8t cDNA (SEQ ID NO: 29) encodes a polypeptide having a molecular weight of approximately 26 kD corresponding to SEQ ID NO:30 (see Figure 15). The 8t polypeptide interacts with potassium channel comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 8t mRNA is expressed predominantly in the heart and the brain. The 8t cDNA is a splice variant of 9q.

Human, rat, monkey, and mouse 9q cDNA were also isolated. Splice variants include human 9ql (SEQ ID NO:13; Figure 7) rat 9ql (SEQ ID NO:15; Figure 8), mouse 9ql (SEQ ID NO:17; Figure 9), human 9qm (SEQ ID NO:19; Figure 10), rat 9qm (SEQ ID NO:21; Figure 11), human 9qs (SEQ ID NO:23; Figure 12), monkey 9qs (SEQ ID NO:25; Figure 13), and rat 9qc (SEQ ID NO:27; Figure 14). The genomic DNA sequence of 9q has also be determined. Exon 1 and its flanking intron sequences (SEQ ID NO:46) are shown in Figure 22A. Exons 2-11 and the flanking intron sequences (SEQ ID NO:47) are shown in Figure 22B. 9q polypeptides interact with potassium

channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 9q proteins are expressed predominantly in the heart and the brain. In the brain, 9q mRNA is highly expressed in the neostriatum, hippocampal formation, neocortical pyramidal cells and interneurons, and in the thalamus, superior colliculus, and cerebellum.

Human, rat, and mouse P19 cDNA was also isolated. Human P19 is shown in SEQ ID NO:31 and Figure 16; and in SEQ ID NO:39 and Figure 20 (the 3' sequence). Rat P19 is shown in SEQ ID NO:33 and Figure 17, and mouse P19 is shown in SEQ ID NO:35 and Figure 18. P19 polypeptides interact with potassium channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot analysis, the P19 transcripts (mRNA) are expressed predominantly in the brain.

A partial human paralog of the PCIP molecules was also identified. This paralog is referred to herein as W28559 and is shown in SEQ ID NO:37 and Figure 19.

Monkey KChIP4a and its splice variants KChIP4b, KChIP4c, and KChIP4d were also identified. Monkey KChIP4a is shown in SEQ ID NO:48 and Figure 23. Monkey KChIP4b is shown in SEQ ID NO:50 and Figure 24. Monkey KChIP4c is shown in SEQ ID NO:69 and Figure 35. Monkey KChIP4d is shown in SEQ ID NO:71 and Figure 36.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ ID NOs:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in length. Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays.

The nucleotide sequence of the full length human 33b07 cDNA and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in SEQ ID NOs:54 and 55, respectively.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length. Rat

1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays.

The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 270 amino acid residues in length. Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays.

The sequences of the present invention are summarized below, in Tables I and II.

10

Table I

Novel Polynucleotides and Polypeptides of the Present Invention (full length except where noted)

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
1v or KChIP1	1v	human (225-875)*	1	2	98994
	1v	rat (210-860)	3	4	98946
	1v	mouse (477-1127)	5	6	98945
	1vl	rat (31-714)	7	8	98942
	1vl	mouse (77-760)	9	10	98943
	1vn (partial)	rat (345-955)	11	12	98944

9q or KChIP2	Genomic DNA sequence (Exon 1 and flanking intron sequences)	human	46		
	Genomic DNA sequence (Exons 2-11 and flanking intron sequences)	human	47		
	9ql	human (207-1019)	13	14	98993 98991
	9ql (partial)	rat (2-775)	15	16	98948
	9ql	mouse (181 -993)	17	18	98937
	9qm	human (207-965)	19	20	98993 98991
	9qm	rat (214-972)	21	22	98941
	9qs	human (207-869)	23	24	98951
	9qs	monkey (133-795)	25	26	98950
	9qc	rat (208-966)	27	28	98947
	8t (partial)	rat (1-678)	29	30	98939

p19 or KChIP3	p19	Human (1-771)	31	32	PTA-316
	p19 (partial)	rat (1-330)	33	34	98936
	p19	mouse (49-819)	35	36	98940
	p193 (partial)	Human (2-127)	39	40	98949
W28559	W28559 (partial)	human (1-339)	37	38	
KChIP4	KChIP4a	Monkey (265-966)	48	49	
	KChIP4b C-terminal splice variant	Monkey (265-966)	50	51	
	KChIP4c splice variant	Monkey (122-811)	69	70	
	KChIP4d splice variant	Monkey (64-816)	71	72	

* The coordinates of the coding sequence are shown in parenthesis. The first column indicates the PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each PCIP.

Table II

Polynucleotides and Polypeptides of the Present Invention (full length except where noted)

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
33b07 Novel	33b07	Human (88-1332)	52	53	PTA-316
	33b07	Rat (85-1308)	54	55	
1p Novel	1p (partial)	Rat (1-804)	56	57	
7s Novel	7s (partial)	Rat (1-813)	58	59	
29x	29x	Rat (433-1071)	60	61	
	25r splice variant of 29x	Rat (130-768)	62		
5p	5p	Rat (52-339)	63	64	
7q	7q	Rat (1-639)	65	66	
19r	19r	Rat (1-816)	67	68	

- 5 * The coordinates of the coding sequence are shown in parenthesis. The first column indicates the four families of PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each family. Novel molecules are also indicated.

Plasmids containing the nucleotide sequences encoding human, rat and monkey PCIPs were deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on November 17, 1998, and assigned the Accession Numbers described above. These deposits will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. These deposits were made merely as a convenience for those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112.

Clones containing cDNA molecules encoding human p19 (clone EphP19) and human 33b07 (clone Eph33b07) were deposited with American Type Culture Collection (Manassas, VA) on July 8, 1998 as Accession Number PTA-316, as part of a composite deposit representing a mixture of two strains, each carrying one recombinant plasmid harboring a particular cDNA clone. (The ATCC strain designation for the mixture of hP19 and h33b07 is EphP19h33b07mix).

To distinguish the strains and isolate a strain harboring a particular cDNA clone, an aliquot of the mixture can be streaked out to single colonies on LB plates supplemented with 100 ug/ml ampicillin, single colonies grown, and then plasmid DNA extracted using a standard miniprep procedure. Next, a sample of the DNA miniprep can be digested with NotI and the resultant products resolved on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest gives the following band patterns: EphP19: 7 kb 9 (single band), Eph33b07: 5.8 kb (single band).

Various aspects of the invention are described in further detail in the following subsections:

25

I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules that encode PCIP proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify PCIP-encoding nucleic acid molecules (*e.g.*, PCIP mRNA) and fragments for use as PCR primers for the amplification or mutation of PCIP nucleic acid molecules. As used herein, the term

30

"nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The

nucleic acid molecule can be single-stranded or double-stranded, but preferably is
5 double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the
10 organism from which the nucleic acid is derived. For example, in various embodiments, the isolated PCIP nucleic acid molecule can contain less than about 5 kb, 4kb, 3kb, 2kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free
15 of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID
20 NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID
25 NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid
30 sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ

ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the
5 nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, as a hybridization probe, PCIP nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, J., Fritsh, E. F.,
10 and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory. Cold Spring Harbor Laboratory Press. Cold Spring Harbor, NY, 1989).

Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11,
15 SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence
20 of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the
25 sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the
30 nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as

Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994.

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers
5 according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to PCIP nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In a preferred embodiment, an isolated nucleic acid molecule of the invention
10 comprises the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID
15 NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion of any of these nucleotide sequences.

20 In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID
25 NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942,
30 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion of any of these nucleotide sequences. A nucleic acid molecule

which is complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, thereby forming a stable duplex.

In still another preferred embodiment, an isolated nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ

ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the entire length of the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion of any of these nucleotide sequences.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, for example a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of a PCIP protein. The nucleotide sequence determined from the cloning of the PCIP gene allows for the generation of probes and primers designed for use in identifying and/or cloning other PCIP family members, as well as PCIP homologues from other species.

The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID

NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, of an anti-

5 sense sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID

10 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, SEQ ID

15 NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID

20 NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In an exemplary embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 350-400,

25 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 949, 950-1000, or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID

30 NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID

NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 5 98950, 98951, 98991, 98993, or 98994.

Probes based on the PCIP nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-
10 factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress a PCIP protein, such as by measuring a level of a PCIP-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting PCIP mRNA levels or determining whether a genomic PCIP gene has been mutated or deleted.

A nucleic acid fragment encoding a "biologically active portion of a PCIP
15 protein" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID
20 NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, which encodes a polypeptide
25 having a PCIP biological activity (the biological activities of the PCIP proteins are described herein), expressing the encoded portion of the PCIP protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the PCIP protein.

The invention further encompasses nucleic acid molecules that differ from the
30 nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17,

SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID

5 NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, due to degeneracy of the genetic code and thus encode the same PCIP proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ

10 ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID

15 NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ

20 ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID

25 NO:70, or SEQ ID NO:72.

In addition to the PCIP nucleotide sequences shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID

30 NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID

NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, it will be appreciated by those skilled in the art
5 that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the PCIP proteins may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the PCIP genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules which include an open reading frame
10 encoding a PCIP protein, preferably a mammalian PCIP protein, and can further include non-coding regulatory sequences, and introns.

Allelic variants of human PCIP include both functional and non-functional PCIP proteins. Functional allelic variants are naturally occurring amino acid sequence variants of the human PCIP protein that maintain the ability to bind a PCIP ligand and/or
15 modulate any of the PCIP activities described herein. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID
20 NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or substitution, deletion or insertion of non-critical residues in non-critical regions of the protein.

Non-functional allelic variants are naturally occurring amino acid sequence
25 variants of the human PCIP protein that do not have the ability to either bind a PCIP ligand and/or modulate any of the PCIP activities described herein. Non-functional allelic variants will typically contain a non-conservative substitution, a deletion, or insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ
30 ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID

NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or a substitution, insertion or deletion in critical residues or critical regions.

The present invention further provides non-human orthologues of the human PCIP protein. Orthologues of the human PCIP protein are proteins that are isolated from non-human organisms and possess the same PCIP ligand binding and/or modulation of potassium channel mediated activities of the human PCIP protein. Orthologues of the human PCIP protein can readily be identified as comprising an amino acid sequence that is substantially identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

Moreover, nucleic acid molecules encoding other PCIP family members and, thus, which have a nucleotide sequence which differs from the PCIP sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 are intended to be within the scope of the invention. For example, another PCIP cDNA can be identified based on the nucleotide sequence of human PCIP. Moreover, nucleic acid molecules encoding PCIP proteins from different species, and thus which have a nucleotide sequence which differs from the PCIP sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID

NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with
5 ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 are intended to be within the scope of the invention. For example, a mouse PCIP cDNA can be identified based on the nucleotide sequence of a human PCIP.

Nucleic acid molecules corresponding to natural allelic variants and homologues
10 of the PCIP cDNAs of the invention can be isolated based on their homology to the PCIP nucleic acids disclosed herein using the cDNAs disclosed herein, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the
15 invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID
20 NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944,
25 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In other embodiment, the nucleic acid is at least 30, 50, 100, 150, 200, 250, 300, 307, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 949, or 950 nucleotides in length. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60%
30 identical to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about

80%, even more preferably at least about 85% or 90% identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization
5 conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50°C, preferably at 55°C, and more preferably at 60°C or 65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1 corresponds to a naturally-occurring nucleic acid molecule. As used herein, a
10 "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In addition to naturally-occurring allelic variants of the PCIP sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO:1, SEQ ID NO:3
15 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID
20 NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, thereby leading to changes in the amino acid sequence of the encoded PCIP proteins, without altering the functional ability of the
25 PCIP proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID
30 NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID

NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 5 98948, 98949, 98950, 98951, 98991, 98993, or 98994. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of PCIP (*e.g.*, the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the PCIP proteins 10 of the present invention, are predicted to be particularly unamenable to alteration. Furthermore, additional amino acid residues that are conserved between the PCIP proteins of the present invention and other members of the PCIP family of proteins are not likely to be amenable to alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules 20 encoding PCIP proteins that contain changes in amino acid residues that are not essential for activity. Such PCIP proteins differ in amino acid sequence from SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 50%, 55%, 60%, 25 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14,

SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID
 5 NO:72.

An isolated nucleic acid molecule encoding a PCIP protein homologous to the protein of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID
 10 NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11,
 15 SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence
 20 of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced into SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ
 25 ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID
 30 NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942,

98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a PCIP protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a PCIP coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for PCIP biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

In a preferred embodiment, a mutant PCIP protein can be assayed for the ability to (1) interact with (*e.g.*, bind to) a potassium channel protein or portion thereof; (2) regulate the phosphorylation state of a potassium channel protein or portion thereof; (3)

associate with (*e.g.*, bind) calcium and, for example, act as a calcium dependent kinase, *e.g.*, phosphorylate a potassium channel in a calcium-dependent manner; (4) associate with (*e.g.*, bind) calcium and, for example, act as a calcium dependent transcription factor; (5) modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) modulate the release of neurotransmitters; (7) modulate membrane excitability; (8) influence the resting potential of membranes; (9) modulate wave forms and frequencies of action potentials; and (10) modulate thresholds of excitation.

In addition to the nucleic acid molecules encoding PCIP proteins described above, another aspect of the invention pertains to isolated nucleic acid molecules which are antisense thereto. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire PCIP coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding PCIP. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding PCIP. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding PCIP disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of PCIP mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of PCIP mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of PCIP mRNA. An antisense oligonucleotide can be, for

example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids. *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a PCIP protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through

specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-*o*-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave PCIP mRNA transcripts to thereby inhibit translation of PCIP mRNA. A ribozyme having specificity for a PCIP-encoding nucleic acid can be designed based upon the nucleotide sequence of a PCIP cDNA disclosed herein (*i.e.*, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID

NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994). For
5 example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a PCIP-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, PCIP mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA
10 molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.

Alternatively, PCIP gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the PCIP (*e.g.*, the PCIP promoter and/or enhancers) to form triple helical structures that prevent transcription of the PCIP gene in target cells. See generally, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-
15 84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15.

In yet another embodiment, the PCIP nucleic acid molecules of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example,
20 the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases
25 are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* *Proc. Natl. Acad. Sci.* 93: 14670-675.

PNAs of PCIP nucleic acid molecules can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of PCIP nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup B. (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *supra*).

10 In another embodiment, PNAs of PCIP can be modified, (*e.g.*, to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of PCIP nucleic acid molecules can be generated which may combine the advantageous properties of PNA
15 and DNA. Such chimeras allow DNA recognition enzymes, (*e.g.*, RNase H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. (1996) *supra*). The synthesis of PNA-DNA
20 chimeras can be performed as described in Hyrup B. (1996) *supra* and Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et al.* (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a
25 stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. *et al.* (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. *et al.* (1975) *Bioorganic Med. Chem. Lett.* 5: 1119-11124).

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.* (1989) *Proc. Natl. Acad. Sci. US* 86:6553-6556; Lemaitre *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; 5 PCT Publication No. W088/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, *e.g.*, Krol *et al.* (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, *e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (*e.g.*, a peptide, hybridization 10 triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

II. Isolated PCIP Proteins and Anti-PCIP Antibodies

One aspect of the invention pertains to isolated PCIP proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens 15 to raise anti-PCIP antibodies. In one embodiment, native PCIP proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, PCIP proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a PCIP protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

20 An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the PCIP protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of PCIP protein in which 25 the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. In one embodiment, the language "substantially free of cellular material" includes preparations of PCIP protein having less than about 30% (by dry weight) of non-PCIP protein (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-PCIP protein, still more preferably less than 30 about 10% of non-PCIP protein, and most preferably less than about 5% non-PCIP protein. When the PCIP protein or biologically active portion thereof is recombinantly

produced, it is also preferably substantially free of culture medium. *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of PCIP protein in which the protein is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of PCIP protein having less than about 30% (by dry weight) of chemical precursors or non-PCIP chemicals, more preferably less than about 20% chemical precursors or non-PCIP chemicals, still more preferably less than about 10% chemical precursors or non-PCIP chemicals, and most preferably less than about 5% chemical precursors or non-PCIP chemicals.

As used herein, a "biologically active portion" of a PCIP protein includes a fragment of a PCIP protein which participates in an interaction between a PCIP molecule and a non-PCIP molecule. Biologically active portions of a PCIP protein include peptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the PCIP protein, *e.g.*, the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, which include less amino acids than the full length PCIP proteins, and exhibit at least one activity of a PCIP protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the PCIP protein, *e.g.*, binding of a potassium channel subunit. A biologically active portion of a PCIP protein can be a polypeptide which is, for example, 10, 25, 50, 100, 200, or more amino acids in length. Biologically active portions of a PCIP protein can be used as targets for developing agents which modulate a potassium channel mediated activity.

In one embodiment, a biologically active portion of a PCIP protein comprises at least one calcium binding domain.

It is to be understood that a preferred biologically active portion of a PCIP protein of the present invention may contain at least one of the above-identified structural domains. A more preferred biologically active portion of a PCIP protein may contain at least two of the above-identified structural domains. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native PCIP protein.

10 In a preferred embodiment, the PCIP protein has an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72. In other embodiments, the PCIP protein is substantially homologous to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, and retains the functional activity of the protein of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection I above. Accordingly, in another embodiment, the PCIP protein is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%,

70%, 75%, 80%, 85%, 90%, 95% or more identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

Isolated proteins of the present invention, preferably 1v, 9q, p19, W28559, KChIP4a, KChIP4b, 33b07, 1p, or 7s proteins, have an amino acid sequence sufficiently identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or are encoded by a nucleotide sequence sufficiently identical to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71. As used herein, the term "sufficiently identical" refers to a first amino acid or nucleotide sequence which contains a sufficient or minimum number of identical or equivalent (*e.g.*, an amino acid residue which has a similar side chain) amino acid residues or nucleotides to a second amino acid or nucleotide sequence such that the first and second amino acid or nucleotide sequences share common structural domains or motifs and/or a common functional activity. For example, amino acid or nucleotide sequences which share common structural domains have at least 30%, 40%, or 50% identity, preferably 60% identity, more preferably 70%-80%, and even more preferably 90-95% identity across the amino acid sequences of the domains and contain at least one and preferably two structural domains or motifs, are defined herein as sufficiently identical. Furthermore, amino acid or nucleotide sequences

which share at least 30%, 40%, or 50%, preferably 60%, more preferably 70-80%, or 90-95% identity and share a common functional activity are defined herein as sufficiently identical.

Preferred proteins are PCIP proteins having at least one calcium binding domain
5 and, preferably, a PCIP activity. Other preferred proteins are PCIP proteins having at least one calcium binding domain, and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID
10 NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71.

15 To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence
20 aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (*e.g.*, when aligning a second sequence to the PCIP amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID
25 NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 having 177 amino acid residues, at least 80, preferably at least 100, more
30 preferably at least 120, even more preferably at least 140, and even more preferably at least 150, 160 or 170 amino acid residues are aligned). The amino acid residues or

nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid

5 "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two

10 sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blosum 62 matrix or a PAM250 matrix, and a gap

15 weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent

20 identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (*CABIOS*, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be

25 used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences

30 homologous to PCIP nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain

amino acid sequences homologous to PCIP protein molecules of the invention. To obtain gapped alignments for comparison purposes. Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective
5 programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

The invention also provides PCIP chimeric or fusion proteins. As used herein, a PCIP "chimeric protein" or "fusion protein" comprises a PCIP polypeptide operatively linked to a non-PCIP polypeptide. An "PCIP polypeptide" refers to a polypeptide having an amino acid sequence corresponding to PCIP, whereas a "non-PCIP
10 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the PCIP protein, *e.g.*, a protein which is different from the PCIP protein and which is derived from the same or a different organism. Within a PCIP fusion protein the PCIP polypeptide can correspond to all or a portion of a PCIP protein. In a preferred embodiment, a PCIP fusion protein comprises
15 at least one biologically active portion of a PCIP protein. In another preferred embodiment, a PCIP fusion protein comprises at least two biologically active portions of a PCIP protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the PCIP polypeptide and the non-PCIP polypeptide are fused in-frame to each other. The non-PCIP polypeptide can be fused to the N-terminus or C-terminus of
20 the PCIP polypeptide.

For example, in one embodiment, the fusion protein is a GST-PCIP fusion protein in which the PCIP sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant PCIP.

In another embodiment, the fusion protein is a PCIP protein containing a
25 heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of PCIP can be increased through use of a heterologous signal sequence.

The PCIP fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The PCIP fusion
30 proteins can be used to affect the bioavailability of a PCIP substrate. Use of PCIP fusion proteins may be useful therapeutically for the treatment of potassium channel

associated disorders such as CNS disorders, *e.g.*, neurodegenerative disorders such as Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; and neurological disorders; *e.g.*, migraine. Use of PCIP fusion proteins may also be useful therapeutically for the treatment of potassium channel associated disorders such as cardiovascular disorders, *e.g.*, arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation or congestive heart failure.

Moreover, the PCIP-fusion proteins of the invention can be used as immunogens to produce anti-PCIP antibodies in a subject, to purify PCIP ligands and in screening assays to identify molecules which inhibit the interaction of PCIP with a PCIP substrate.

Preferably, a PCIP chimeric or fusion protein of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A PCIP-

encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the PCIP protein.

The present invention also pertains to variants of the PCIP proteins which function as either PCIP agonists (mimetics) or as PCIP antagonists. Variants of the PCIP proteins can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation of a PCIP protein. An agonist of the PCIP proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a PCIP protein. An antagonist of a PCIP protein can inhibit one or more of the activities of the naturally occurring form of the PCIP protein by, for example, competitively modulating a potassium channel mediated activity of a PCIP protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the PCIP protein.

In one embodiment, variants of a PCIP protein which function as either PCIP agonists (mimetics) or as PCIP antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of a PCIP protein for PCIP protein agonist or antagonist activity. In one embodiment, a variegated library of PCIP variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of PCIP variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential PCIP sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of PCIP sequences therein. There are a variety of methods which can be used to produce libraries of potential PCIP variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential PCIP sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev.*

Biochem. 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477.

In addition, libraries of fragments of a PCIP protein coding sequence can be used to generate a variegated population of PCIP fragments for screening and subsequent
5 selection of variants of a PCIP protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a PCIP coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked
10 products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the PCIP protein.

Several techniques are known in the art for screening gene products of
15 combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of PCIP proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library
20 into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in
25 combination with the screening assays to identify PCIP variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

In one embodiment, cell based assays can be exploited to analyze a variegated PCIP library. For example, a library of expression vectors can be transfected into a cell
30 line which ordinarily possesses a potassium channel mediated activity. The effect of the PCIP mutant on the potassium channel mediated activity can then be detected, *e.g.*, by

any of a number of enzymatic assays or by detecting the release of a neurotransmitter. Plasmid DNA can then be recovered from the cells which score for inhibition, or alternatively, potentiation of the potassium channel mediated activity, and the individual clones further characterized.

5 An isolated PCIP protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind PCIP using standard techniques for polyclonal and monoclonal antibody preparation. A full-length PCIP protein can be used or, alternatively, the invention provides antigenic peptide fragments of PCIP for use as immunogens. The antigenic peptide of PCIP comprises at least 8 amino acid
10 residues of the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID
15 NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 and encompasses an epitope of PCIP such that an antibody raised against the peptide forms a specific immune complex with PCIP. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid
20 residues.

Preferred epitopes encompassed by the antigenic peptide are regions of PCIP that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

A PCIP immunogen typically is used to prepare antibodies by immunizing a
25 suitable subject, (*e.g.*, rabbit, goat, mouse or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed PCIP protein or a chemically synthesized PCIP polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an
30 immunogenic PCIP preparation induces a polyclonal anti-PCIP antibody response.

Accordingly, another aspect of the invention pertains to anti-PCIP antibodies. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen, such as PCIP. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind PCIP. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of PCIP. A monoclonal antibody composition thus typically displays a single binding affinity for a particular PCIP protein with which it immunoreacts.

Polyclonal anti-PCIP antibodies can be prepared as described above by immunizing a suitable subject with a PCIP immunogen. The anti-PCIP antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized PCIP. If desired, the antibody molecules directed against PCIP can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the anti-PCIP antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985), *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally R. H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum

Publishing Corp., New York, New York (1980); E. A. Lerner (1981) *Yale J. Biol. Med.*, 54:387-402; M. L. Gefter *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a PCIP immunogen as described above, and the culture
5 supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds PCIP.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-PCIP monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.*
10 *Somatic Cell Genet.*, cited *supra*; Lerner, *Yale J. Biol. Med.*, cited *supra*; Kenneth, *Monoclonal Antibodies*, cited *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made
15 by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques,
20 *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days
25 because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind PCIP, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-PCIP antibody can be identified and isolated by screening a
30 recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with PCIP to thereby isolate immunoglobulin library members that bind PCIP.

Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* *Nature* (1990) 348:552-554.

Additionally, recombinant anti-PCIP antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985)

Nature 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

5 An anti-PCIP antibody (*e.g.*, monoclonal antibody) can be used to isolate PCIP by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-PCIP antibody can facilitate the purification of natural PCIP from cells and of recombinantly produced PCIP expressed in host cells. Moreover, an anti-PCIP antibody can be used to detect PCIP protein (*e.g.*, in a cellular lysate or cell supernatant) in order
10 to evaluate the abundance and pattern of expression of the PCIP protein. Anti-PCIP antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various
15 enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include
20 umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

25

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a PCIP protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting
30 another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA

segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other
5 vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are
10 often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

15 The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant
20 expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control
25 elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*,
30 tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the

host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, PCIP proteins, mutant forms of PCIP proteins, fusion proteins, and the like).

The recombinant expression vectors of the invention can be designed for expression of PCIP proteins in prokaryotic or eukaryotic cells. For example, PCIP proteins can be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Purified fusion proteins can be utilized in PCIP activity assays, (*e.g.*, direct assays or competitive assays described in detail below), or to generate antibodies specific for PCIP proteins, for example. In a preferred embodiment, a PCIP fusion

protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (*e.g.*, six (6) weeks).

5 Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 60-89). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene
10 expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

15 One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Another
20 strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, (1992) *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

 In another embodiment, the PCIP expression vector is a yeast expression vector.
25 Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari, *et al.*, (1987) *Embo J.* 6:229-234), pMFa (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz *et al.*, (1987) *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and picZ (InVitrogen Corp, San Diego, CA).

Alternatively, PCIP proteins can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.* (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers (1989) *Virology* 170:31-39).

5 In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements.

10 For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J., Fritsch, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY,*

15 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable

20 tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.* (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.* (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters

25 (*e.g.*, the neurofilament promoter; Byrne and Ruddle (1989) *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.* (1985) *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters

30 (Kessel and Gruss (1990) *Science* 249:374-379) and the α -fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

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The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to PCIP mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a PCIP protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including

calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor
5 Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is
10 generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding a PCIP protein or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic
15 acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a PCIP protein. Accordingly, the invention further provides methods for producing a PCIP protein using the host cells of
20 the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a PCIP protein has been introduced) in a suitable medium such that a PCIP protein is produced. In another embodiment, the method further comprises isolating a PCIP protein from the medium or the host cell.

25 The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which PCIP-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous PCIP sequences have been introduced into their genome or
30 homologous recombinant animals in which endogenous PCIP sequences have been altered. Such animals are useful for studying the function and/or activity of a PCIP and

for identifying and/or evaluating modulators of PCIP activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous PCIP gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a PCIP-encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The PCIP cDNA sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human PCIP gene, such as a mouse or rat PCIP gene, can be used as a transgene. Alternatively, a PCIP gene homologue, such as another PCIP family member, can be isolated based on hybridization to the PCIP cDNA sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID

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NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 (described further in subsection I above) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a PCIP transgene to direct expression of a PCIP protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a PCIP transgene in its genome and/or expression of PCIP mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a PCIP protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a PCIP gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the PCIP gene. The PCIP gene can be a human gene (*e.g.*, the cDNA of SEQ ID NO:1), but more preferably, is a non-human homologue of a human PCIP gene (*e.g.*, the cDNA of SEQ ID NO:3 or 5). For example, a mouse PCIP gene can be used to construct a homologous recombination vector suitable for altering an endogenous PCIP gene in the mouse genome. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous PCIP gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous PCIP gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the

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upstream regulatory region can be altered to thereby alter the expression of the endogenous PCIP protein). In the homologous recombination vector, the altered portion of the PCIP gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the PCIP gene to allow for homologous recombination to occur between the exogenous

5 PCIP gene carried by the vector and an endogenous PCIP gene in an embryonic stem cell. The additional flanking PCIP nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see

10 *e.g.*, Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced PCIP gene has homologously recombined with the endogenous PCIP gene are selected (see *e.g.*, Li, E.

15 *et al.* (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in

20 *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by

25 germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

30 In another embodiment, transgenic non-humans animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the

transgene. animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, *e.g.*, a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G₀ phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, *e.g.*, the somatic cell, is isolated.

IV. Pharmaceutical Compositions

The PCIP nucleic acid molecules, fragments of PCIP proteins, and anti-PCIP antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions
5 used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic
10 acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

15 Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In
20 all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid
25 polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol,
30 ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium

chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active
5 compound (*e.g.*, a fragment of a PCIP protein or an anti-PCIP antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In
10 the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They
15 can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically
20 compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant
25 such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant,
30 *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7

5 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

The present invention encompasses agents which modulate expression
10 or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (i.e., including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic
15 or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such
20 compounds.

It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending
25 upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about
30 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams

per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram.

It is

furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated.

- 5 Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate
- 10 response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be
- 15 modulated.

- Further, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include
- 20 taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil
- 25 decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin,
- 30 mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin
5 such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha.-interferon, beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"),
10 granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug
15 Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in
20 *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S.
25 Patent No. 4,676,980.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by stereotactic injection (see *e.g.*, Chen *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-
30 3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which

the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

- 5 The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

V. Uses and Methods of the Invention

- The nucleic acid molecules, proteins, protein homologues, and antibodies
- 10 described herein can be used in one or more of the following methods: a) screening assays; b) predictive medicine (*e.g.*, diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenetics); and c) methods of treatment (*e.g.*, therapeutic and prophylactic). As described herein, a PCIP protein of the invention has one or more of the following activities: (1) it interacts with (*e.g.*, binds to) a potassium channel protein
- 15 or portion thereof; (2) it regulates the phosphorylation state of a potassium channel protein or portion thereof; (3) it associates with (*e.g.*, binds to) calcium and can, for example, act as a calcium dependent kinase, *e.g.*, phosphorylate a potassium channel or a G-protein coupled receptor in a calcium-dependent manner; (4) it associates with (*e.g.*, binds to) calcium and can, for example, act as a calcium dependent transcription factor;
- 20 (5) it modulates a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) it modulates chromatin formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) it modulates vesicular traffic and protein transport in a cell, *e.g.*, a neuronal or cardiac cell; (8) it modulates cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell; (9) it regulates the association of a
- 25 potassium channel protein or portion thereof with the cellular cytoskeleton; (10) it modulates cellular proliferation; (11) it modulates the release of neurotransmitters; (12) it modulates membrane excitability; (13) it influences the resting potential of membranes; (14) it modulates wave forms and frequencies of action potentials; and (15) it modulates thresholds of excitation and, thus, can be used to, for example, (1) modulate
- 30 the activity of a potassium channel protein or portion thereof; (2) modulate the phosphorylation state of a potassium channel protein or portion thereof; (3) modulate the

phosphorylation state of a potassium channel or a G-protein coupled receptor in a calcium-dependent manner; (4) associate with (*e.g.*, bind to) calcium and act as a calcium dependent transcription factor; (5) modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) modulate chromatin formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) modulate vesicular traffic and protein transport in a cell, *e.g.*, a neuronal or cardiac cell; (8) modulate cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell; (9) regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) modulate cellular proliferation; (11) modulate the release of neurotransmitters; (12) modulate membrane excitability; (13) influence the resting potential of membranes; (14) modulate wave forms and frequencies of action potentials; and (15) modulate thresholds of excitation.

The isolated nucleic acid molecules of the invention can be used, for example, to express PCIP protein (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect PCIP mRNA (*e.g.*, in a biological sample) or a genetic alteration in a PCIP gene, and to modulate PCIP activity, as described further below. The PCIP proteins can be used to treat disorders characterized by insufficient or excessive production of a PCIP substrate or production of PCIP inhibitors. In addition, the PCIP proteins can be used to screen for naturally occurring PCIP substrates, to screen for drugs or compounds which modulate PCIP activity, as well as to treat disorders characterized by insufficient or excessive production of PCIP protein or production of PCIP protein forms which have decreased or aberrant activity compared to PCIP wild type protein (*e.g.*, CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma;

or cardiovascular disorders such as sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia). Moreover, the anti-PCIP antibodies of the invention can be used to detect
5 and isolate PCIP proteins, regulate the bioavailability of PCIP proteins, and modulate PCIP activity.

A. Screening Assays:

The invention provides a method (also referred to herein as a "screening assay")
10 for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) which bind to PCIP proteins, have a stimulatory or inhibitory effect on, for example, PCIP expression or PCIP activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of PCIP substrate.

15 In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a PCIP protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a PCIP protein or polypeptide or biologically active portion thereof. The test compounds of the present
20 invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is
25 limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem.*
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Int. Ed. Engl. 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor
5 (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP
'409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage
(Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406);
(Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.*
222:301-310); (Ladner *supra.*).

10. In one embodiment, an assay is a cell-based assay in which a cell which
expresses a PCIP protein or biologically active portion thereof is contacted with a test
compound and the ability of the test compound to modulate PCIP activity, *e.g.*, binding
to a potassium channel or a portion thereof, is determined. Determining the ability of
the test compound to modulate PCIP activity can be accomplished by monitoring, for
15 example, the release of a neurotransmitter, *e.g.*, dopamine, from a cell which expresses
PCIP such as a neuronal cell, *e.g.*, a substantia nigra neuronal cell, or a cardiac cell.
Furthermore, determining the ability of the test compound to modulate PCIP activity can
be accomplished by monitoring, for example, the I_{to} current or the release of a
neurotransmitter from a cell which expresses PCIP such as a cardiac cell. Currents in
20 cells, *e.g.*, the I_{to} current, can be measured using the patch-clamp technique as described
in the Examples section using the techniques described in, for example, Hamill *et al.*
1981. *Pfluegers Arch.* 391: 85-100). The cell, for example, can be of mammalian origin.
Determining the ability of the test compound to modulate the ability of PCIP to bind to a
substrate can be accomplished, for example, by coupling the PCIP substrate with a
25 radioisotope or enzymatic label such that binding of the PCIP substrate to PCIP can be
determined by detecting the labeled PCIP substrate in a complex. For example,
compounds (*e.g.*, PCIP substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either
directly or indirectly, and the radioisotope detected by direct counting of
radioemmission or by scintillation counting. Alternatively, compounds can be
30 enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase,

or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is also within the scope of this invention to determine the ability of a compound (*e.g.*, PCIP substrate) to interact with PCIP without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with PCIP without the labeling of either the compound or the PCIP.

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McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction

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between a compound and PCIP.

In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a PCIP target molecule (*e.g.*, a potassium channel or a fragment thereof) with a test compound and determining the ability of the test compound to modulate (*e.g.* stimulate or inhibit) the activity of the PCIP target molecule. Determining the ability of the test compound to modulate the activity of a PCIP target molecule can be accomplished, for example, by determining the ability of the PCIP protein to bind to or interact with the PCIP target molecule, *e.g.*, a potassium channel or a fragment thereof.

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Determining the ability of the PCIP protein or a biologically active fragment thereof, to bind to or interact with a PCIP target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, determining the ability of the PCIP protein to bind to or interact with a PCIP target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular Ca^{2+} , diacylglycerol, IP_3 , and the like), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter.

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In yet another embodiment, an assay of the present invention is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to bind to the PCIP protein or biologically active portion thereof is determined. Preferred biologically active portions of the PCIP proteins to be used in assays of the present invention include fragments which participate in interactions with non-PCIP molecules, *e.g.*, potassium channels or fragments thereof, or fragments with high surface probability scores. Binding of the test compound to the PCIP protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the PCIP protein or biologically active portion thereof with a known compound which binds PCIP to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a PCIP protein, wherein determining the ability of the test compound to interact with a PCIP protein comprises determining the ability of the test compound to preferentially bind to PCIP or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the PCIP protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a PCIP protein can be accomplished, for example, by determining the ability of the PCIP protein to bind to a PCIP target molecule by one of the methods described above for determining direct binding. Determining the ability of the PCIP protein to bind to a PCIP target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA). Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705. As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a PCIP protein can be accomplished by determining the ability of the PCIP protein to further modulate the activity of a downstream effector of a PCIP target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

In yet another embodiment, the cell-free assay involves contacting a PCIP protein or biologically active portion thereof with a known compound which binds the PCIP protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the PCIP protein, wherein determining the ability of the test compound to interact with the PCIP protein comprises determining the ability of the PCIP protein to preferentially bind to or modulate the activity of a PCIP target molecule.

The cell-free assays of the present invention are amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (*e.g.*, a potassium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton[®] X-100, Triton[®] X-114, Thesit[®], Isotridecypoly(ethylene glycol ether)_n, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl=N,N-dimethyl-3-ammonio-1-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either PCIP or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a PCIP protein, or interaction of a PCIP protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates,

test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/ PCIP fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads
5 (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or PCIP protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound
10 components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of PCIP binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the
15 screening assays of the invention. For example, either a PCIP protein or a PCIP target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated PCIP protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well
20 plates (Pierce Chemical). Alternatively, antibodies reactive with PCIP protein or target molecules but which do not interfere with binding of the PCIP protein to its target molecule can be derivatized to the wells of the plate, and unbound target or PCIP protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include
25 immunodetection of complexes using antibodies reactive with the PCIP protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the PCIP protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate vesicular traffic
30 and protein transport in a cell, *e.g.*, a neuronal or cardiac cell, using the assays described in, for example, Komada M. *et al.* (1999) *Genes Dev.*13(11):1475-85, and Roth M.G. *et*

al. (1999) *Chem. Phys. Lipids*. 98(1-2):141-52. the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to regulate the phosphorylation state of a potassium channel protein or portion thereof, using for example, an *in vitro* kinase assay. Briefly, a PCIP target molecule, *e.g.*, an immunoprecipitated potassium channel from a cell line expressing such a molecule, can be incubated with the PCIP protein and radioactive ATP, *e.g.*, [γ - ^{32}P] ATP, in a buffer containing MgCl_2 and MnCl_2 , *e.g.*, 10 mM MgCl_2 and 5 mM MnCl_2 . Following the incubation, the immunoprecipitated PCIP target molecule, *e.g.*, the potassium channel, can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, *e.g.*, a PVDF membrane, and autoradiographed. The appearance of detectable bands on the autoradiograph indicates that the PCIP substrate, *e.g.*, the potassium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the PCIP substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards. Assays such as those described in, for example, Tamaskovic R. *et al.* (1999) *Biol. Chem.* 380(5):569-78, the contents of which are incorporated herein by reference, can also be used.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to associate with (*e.g.*, bind) calcium, using for example, the assays described in Liu L. (1999) *Cell Signal*. 11(5):317-24 and Kawai T. *et al.* (1999) *Oncogene* 18(23):3471-80, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate chromatin formation in a cell, using for example, the assays described in Okuwaki M. *et*

al. (1998) *J. Biol. Chem.* 273(51):34511-8 and Miyaji-Yamaguchi M. (1999) *J. Mol. Biol.* 290(2): 547-557, the contents of which are incorporated herein by reference.

In yet another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate cellular proliferation, using for example, the assays described in Baker F.L. *et al.* (1995) *Cell Prolif.* 28(1):1-15, Cheviron N. *et al.* (1996) *Cell Prolif.* 29(8):437-46. Hu Z.W. *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290(1):28-37 and Elliott K. *et al.* (1999) *Oncogene* 18(24):3564-73, the contents of which are incorporated herein by reference.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton, using for example, the assays described in Gonzalez C. *et al.* (1998) *Cell Mol. Biol.* 44(7):1117-27 and Chia C.P. *et al.* (1998) *Exp. Cell Res.* 244(1):340-8, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. *et al.* (1985) *J. Biol. Chem.* 260(8):4740-4 and Barker J.L. *et al.* (1984) *Neurosci. Lett.* 47(3):313-8, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell, the assays described in Nakashima Y. *et al.* (1999) *J. Bone Joint Surg. Am.* 81(5):603-15, the contents of which are incorporated herein by reference.

In another embodiment, modulators of PCIP expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of PCIP mRNA or protein in the cell is determined. The level of expression of PCIP mRNA or protein in the presence of the candidate compound is compared to the level of expression of PCIP mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of PCIP expression based on this comparison. For example, when expression of PCIP mRNA or protein is greater

(statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of PCIP mRNA or protein expression. Alternatively, when expression of PCIP mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of PCIP mRNA or protein expression. The level of PCIP mRNA or protein expression in the cells can be determined by methods described herein for detecting PCIP mRNA or protein.

In yet another aspect of the invention, the PCIP proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with PCIP ("PCIP-binding proteins" or "PCIP-bp") and are involved in PCIP activity (described in more detail in the Examples section below).

Such PCIP-binding proteins are also likely to be involved in the propagation of signals by the PCIP proteins or PCIP targets as, for example, downstream elements of a PCIP-mediated signaling pathway. Alternatively, such PCIP-binding proteins are likely to be PCIP inhibitors.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a PCIP protein is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a PCIP-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies

containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the PCIP protein.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a PCIP modulating agent, an antisense PCIP nucleic acid molecule, a PCIP-specific antibody, or a PCIP-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments, *e.g.*, treatments of a CNS disorder or a cardiovascular disorder, as described herein.

15 B. Detection Assays

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. These applications are described in the subsections below.

1. Chromosome Mapping

25 Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. This process is called chromosome mapping. Accordingly, portions or fragments of the PCIP nucleotide sequences, described herein, can be used to map the location of the PCIP genes on a chromosome. The mapping of the PCIP sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, PCIP genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the PCIP nucleotide sequences. Computer analysis of the PCIP sequences can be used to predict primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers
5 can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the PCIP sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (*e.g.*, human and mouse cells). As hybrids of human and mouse cells grow
10 and divide, they gradually lose human chromosomes in random order, but retain the mouse chromosomes. By using media in which mouse cells cannot grow, because they lack a particular enzyme, but human cells can, the one human chromosome that contains the gene encoding the needed enzyme, will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single
15 human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. (D'Eustachio P. *et al.* (1983) *Science* 220:919-924). Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

20 PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the PCIP nucleotide sequences to design oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes. Other mapping strategies which can similarly be
25 used to map a PCIP sequence to its chromosome include *in situ* hybridization (described in Fan, Y. *et al.* (1990) *Proc. Natl. Acad. Sci. USA*, 87:6223-27), pre-screening with labeled flow-sorted chromosomes, and pre-selection by hybridization to chromosome specific cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase
30 chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been

blocked in metaphase by a chemical such as colcemid that disrupts the mitotic spindle. The chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be used with a DNA sequence
5 as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases will suffice to get good results at a reasonable amount of time. For a review of this technique, see Verma *et al.*, Human Chromosomes: A Manual of Basic Techniques
10 (Pergamon Press, New York 1988).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding
15 sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in
20 Man, available on-line through Johns Hopkins University Welch Medical Library). The relationship between a gene and a disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, for example, Egeland, J. *et al.* (1987) *Nature*, 325:783-787.

Moreover, differences in the DNA sequences between individuals affected and
25 unaffected with a disease associated with the PCIP gene, can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are
30 visible from chromosome spreads or detectable using PCR based on that DNA sequence.

Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

5 2. Tissue Typing

The PCIP sequences of the present invention can also be used to identify individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is
10 digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The sequences of the present invention are useful as additional DNA markers for RFLP (described in U.S. Patent 5,272,057).

15 Furthermore, the sequences of the present invention can be used to provide an alternative technique which determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the PCIP nucleotide sequences described herein can be used to prepare two PCR primers from the 5' and 3' ends of the sequences. These primers can then be used to amplify an individual's DNA and
20 subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the present invention can be used to obtain such identification sequences from individuals
25 and from tissue. The PCIP nucleotide sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Each of the sequences described herein can, to some
30 degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the

noncoding regions, fewer sequences are necessary to differentiate individuals. Non-coding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences are used, a more appropriate number of primers for
5 positive individual identification would be 500-2,000.

If a panel of reagents from PCIP nucleotide sequences described herein is used to generate a unique identification database for an individual, those same reagents can later be used to identify tissue from that individual. Using the unique identification database, positive identification of the individual, living or dead, can be made from extremely
10 small tissue samples.

3. Use of Partial PCIP Sequences in Forensic Biology

DNA-based identification techniques can also be used in forensic biology. Forensic biology is a scientific field employing genetic typing of biological evidence found at a crime scene as a means for positively identifying, for example, a perpetrator
15 of a crime. To make such an identification, PCR technology can be used to amplify DNA sequences taken from very small biological samples such as tissues, *e.g.*, hair or skin, or body fluids, *e.g.*, blood, saliva, or semen found at a crime scene. The amplified sequence can then be compared to a standard, thereby allowing identification of the
20 origin of the biological sample.

The sequences of the present invention can be used to provide polynucleotide reagents, *e.g.*, PCR primers, targeted to specific loci in the human genome, which can enhance the reliability of DNA-based forensic identifications by, for example, providing another "identification marker" (*i.e.* another DNA sequence that is unique to a particular
25 individual). As mentioned above, actual base sequence information can be used for identification as an accurate alternative to patterns formed by restriction enzyme generated fragments. Sequences targeted to noncoding regions are particularly appropriate for this use as greater numbers of polymorphisms occur in the noncoding regions, making it easier to differentiate individuals using this technique. Examples of
30 polynucleotide reagents include the PCIP nucleotide sequences or portions thereof, having a length of at least 20 bases, preferably at least 30 bases.

The PCIP nucleotide sequences described herein can further be used to provide polynucleotide reagents, *e.g.*, labeled or labelable probes which can be used in, for example, an *in situ* hybridization technique, to identify a specific tissue, *e.g.*, brain tissue. This can be very useful in cases where a forensic pathologist is presented with a tissue of unknown origin. Panels of such PCIP probes can be used to identify tissue by species and/or by organ type.

In a similar fashion, these reagents, *e.g.*, PCIP primers or probes can be used to screen tissue culture for contamination (*i.e.* screen for the presence of a mixture of different types of cells in a culture).

C. Predictive Medicine:

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically.

Accordingly, one aspect of the present invention relates to diagnostic assays for determining PCIP protein and/or nucleic acid expression as well as PCIP activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant PCIP expression or activity. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with PCIP protein, nucleic acid expression or activity. For example, mutations in a PCIP gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with PCIP protein, nucleic acid expression or activity.

Another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of PCIP in clinical trials.

These and other agents are described in further detail in the following sections.

1. Diagnostic Assays

An exemplary method for detecting the presence or absence of PCIP protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of
5 detecting PCIP protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes PCIP protein such that the presence of PCIP protein or nucleic acid is detected in the biological sample. A preferred agent for detecting PCIP mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to PCIP mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length PCIP nucleic acid, such as the
10 nucleic acid of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
15 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and
20 sufficient to specifically hybridize under stringent conditions to PCIP mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

A preferred agent for detecting PCIP protein is an antibody capable of binding to PCIP protein, preferably an antibody with a detectable label. Antibodies can be
25 polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is
30 directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with

biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect PCIP mRNA, protein, or

5 genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of PCIP mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of PCIP protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of PCIP genomic DNA include

10 Southern hybridizations. Furthermore, *in vivo* techniques for detection of PCIP protein include introducing into a subject a labeled anti-PCIP antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the

15 test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a serum sample or cerebrospinal fluid isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control

20 biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting PCIP protein, mRNA, or genomic DNA, such that the presence of PCIP protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of PCIP protein, mRNA or genomic DNA in the control sample with the presence of PCIP protein, mRNA or genomic DNA in the test

25 sample.

The invention also encompasses kits for detecting the presence of PCIP in a biological sample. For example, the kit can comprise a labeled compound or agent capable of detecting PCIP protein or mRNA in a biological sample; means for determining the amount of PCIP in the sample; and means for comparing the amount of

30 PCIP in the sample with a standard. The compound or agent can be packaged in a

suitable container. The kit can further comprise instructions for using the kit to detect PCIP protein or nucleic acid.

2. Prognostic Assays

5 The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant PCIP expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with a misregulation in PCIP
10 protein activity or nucleic acid expression, such as a neurodegenerative disorder, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; a psychiatric disorder, *e.g.*, depression, schizophrenic
15 disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; a learning or memory disorder, *e.g.*, amnesia or age-related memory loss; a neurological disorder, *e.g.*, migraine; a pain disorder, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or a cardiovascular disorder, *e.g.*, sinus node disfunction, angina, heart failure,
20 hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia.

Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disorder associated with a misregulation in PCIP protein activity
25 or nucleic acid expression, such as a potassium channel associated disorder. Thus, the present invention provides a method for identifying a disease or disorder associated with aberrant PCIP expression or activity in which a test sample is obtained from a subject and PCIP protein or nucleic acid (*e.g.*, mRNA or genomic DNA) is detected, wherein the presence of PCIP protein or nucleic acid is diagnostic for a subject having or at risk
30 of developing a disease or disorder associated with aberrant PCIP expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of

interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant PCIP expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a CNS disorder or a cardiovascular disorder. Thus, the present invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant PCIP expression or activity in which a test sample is obtained and PCIP protein or nucleic acid expression or activity is detected (*e.g.*, wherein the abundance of PCIP protein or nucleic acid expression or activity is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant PCIP expression or activity).

The methods of the invention can also be used to detect genetic alterations in a PCIP gene, thereby determining if a subject with the altered gene is at risk for a disorder characterized by misregulation in PCIP protein activity or nucleic acid expression, such as a CNS disorder or a cardiovascular disorder. In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic alteration characterized by at least one of an alteration affecting the integrity of a gene encoding a PCIP-protein, or the mis-expression of the PCIP gene. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a PCIP gene; 2) an addition of one or more nucleotides to a PCIP gene; 3) a substitution of one or more nucleotides of a PCIP gene, 4) a chromosomal rearrangement of a PCIP gene; 5) an alteration in the level of a messenger RNA transcript of a PCIP gene, 6) aberrant modification of a PCIP gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a PCIP gene, 8) a non-wild type level of a PCIP-protein, 9) allelic loss of a PCIP gene, and 10) inappropriate post-translational modification of a PCIP-protein. As described herein, there are a large number of assays known in the art which can be used for detecting alterations in a PCIP

gene. A preferred biological sample is a tissue or serum sample isolated by conventional means from a subject.

In certain embodiments, detection of the alteration involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, *e.g.*, U.S. Patent Nos. 5 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR. or, alternatively, in a ligation chain reaction (LCR) (see, *e.g.*, Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in the PCIP-gene (see Abravaya *et al.* (1995) *Nucleic Acids Res.* 23:675-682). This method can include the steps of 10 collecting a sample of cells from a subject, isolating nucleic acid (*e.g.*, genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a PCIP gene under conditions such that hybridization and amplification of the PCIP-gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the 15 amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.*, (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional 20 amplification system (Kwoh, D.Y. *et al.*, (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such 25 molecules are present in very low numbers.

In an alternative embodiment, mutations in a PCIP gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel 30 electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence

specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in PCIP can be identified by

5 hybridizing a sample and control nucleic acids, *e.g.*, DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotide probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7: 244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2: 753-759). For example, genetic mutations in PCIP can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al. supra*.

10 Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe

15 arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the PCIP gene and detect mutations by

20 comparing the sequence of the sample PCIP with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert ((1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger ((1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the

25 diagnostic assays ((1995) *Biotechniques* 19:448), including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

Other methods for detecting mutations in the PCIP gene include methods in

30 which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the

art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type PCIP sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex
5 such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched
10 regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397; Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

15 In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in PCIP cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase
20 from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a PCIP sequence, *e.g.*, a wild-type PCIP sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the
25 like. See, for example, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in PCIP genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci*
30 *USA*: 86:2766, see also Cotton (1993) *Mutat. Res.* 285:125-144; and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and

control PCIP nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

10 In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3'

end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain
5 embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

10 The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.*, in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a PCIP gene.

15 Furthermore, any cell type or tissue in which PCIP is expressed may be utilized in the prognostic assays described herein.

3. Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (*e.g.*, drugs) on the expression or activity of a
20 PCIP protein (*e.g.*, the modulation of membrane excitability or resting potential) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase PCIP gene expression, protein levels, or upregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting decreased PCIP gene expression, protein levels, or
25 downregulated PCIP activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease PCIP gene expression, protein levels, or downregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting increased PCIP gene expression, protein levels, or upregulated PCIP activity. In such clinical trials, the expression or activity of a PCIP gene, and preferably, other genes that have been
30 implicated in, for example, a potassium channel associated disorder can be used as a "read out" or markers of the phenotype of a particular cell.

For example, and not by way of limitation, genes, including PCIP, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) which modulates PCIP activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on potassium channel associated disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of PCIP and other genes implicated in the potassium channel associated disorder, respectively. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of PCIP or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during treatment of the individual with the agent.

In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a PCIP protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the pre-administration sample with the PCIP protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of PCIP to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of PCIP to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an

embodiment, PCIP expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

D. Methods of Treatment:

- 5 The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant PCIP expression or activity. With regards to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.
- 10 "Pharmacogenomics", as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype".) Thus, another aspect of the
- 15 invention provides methods for tailoring an individual's prophylactic or therapeutic treatment with either the PCIP molecules of the present invention or PCIP modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will
- 20 experience toxic drug-related side effects.

1. Prophylactic Methods

- In one aspect, the invention provides a method for preventing in a subject, a disease or condition associated with an aberrant PCIP expression or activity, by
- 25 administering to the subject a PCIP or an agent which modulates PCIP expression or at least one PCIP activity. Subjects at risk for a disease which is caused or contributed to by aberrant PCIP expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the
- 30 PCIP aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of PCIP aberrancy, for example, a PCIP, PCIP

agonist or PCIP antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

2. Therapeutic Methods

5 Another aspect of the invention pertains to methods of modulating PCIP expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a PCIP or agent that modulates one or more of the activities of PCIP protein activity associated with the cell. An agent that modulates PCIP protein activity can be an agent
10 as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a PCIP protein (*e.g.*, a PCIP substrate), a PCIP antibody, a PCIP agonist or antagonist, a peptidomimetic of a PCIP agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more PCIP activities. Examples of such stimulatory agents include active PCIP protein and a nucleic acid molecule encoding
15 PCIP that has been introduced into the cell. In another embodiment, the agent inhibits one or more PCIP activities. Examples of such inhibitory agents include antisense PCIP nucleic acid molecules, anti-PCIP antibodies, and PCIP inhibitors. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the present
20 invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of a PCIP protein or nucleic acid molecule. Examples of such disorders include CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis,
25 amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain
30 associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders, *e.g.*, arteriosclerosis, ischemia reperfusion injury, restenosis,

- arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina,
- 5 heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, upregulates or downregulates) PCIP expression or activity.
- 10 In another embodiment, the method involves administering a PCIP protein or nucleic acid molecule as therapy to compensate for reduced or aberrant PCIP expression or activity.

A preferred embodiment of the present invention involves a method for treatment of a PCIP associated disease or disorder which includes the step of administering a

15 therapeutically effective amount of a PCIP antibody to a subject. As defined herein, a therapeutically effective amount of antibody (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The

20 skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of an antibody can include a single treatment or, preferably, can include a series

25 of treatments. In a preferred example, a subject is treated with antibody in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody used for treatment may increase or decrease over

30 the course of a particular treatment. Changes in dosage may result from the results of diagnostic assays as described herein.

Stimulation of PCIP activity is desirable in situations in which PCIP is abnormally downregulated and/or in which increased PCIP activity is likely to have a beneficial effect. For example, stimulation of PCIP activity is desirable in situations in which a PCIP is downregulated and/or in which increased PCIP activity is likely to have a beneficial effect. Likewise, inhibition of PCIP activity is desirable in situations in which PCIP is abnormally upregulated and/or in which decreased PCIP activity is likely to have a beneficial effect.

3. Pharmacogenomics

The PCIP molecules of the present invention, as well as agents, or modulators which have a stimulatory or inhibitory effect on PCIP activity (*e.g.*, PCIP gene expression) as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) potassium channel associated disorders associated with aberrant PCIP activity (*e.g.*, CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders such as arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype

and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a PCIP molecule or PCIP modulator as well as tailoring the dosage and/or therapeutic regimen of treatment with a PCIP molecule or PCIP modulator.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp. Pharmacol. Physiol.* 23(10-11) :983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants.) Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten-million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of

DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

Alternatively, a method termed the "candidate gene approach", can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug's target is known (*e.g.*, a PCIP protein of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Alternatively, a method termed the "gene expression profiling", can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (*e.g.*, a PCIP molecule or PCIP modulator of the present invention) can give an indication whether gene pathways related to toxicity have been
5 turned on.

Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment an individual. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus
10 enhance therapeutic or prophylactic efficiency when treating a subject with a PCIP molecule or PCIP modulator, such as a modulator identified by one of the exemplary screening assays described herein.

This invention is further illustrated by the following examples which should not
15 be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures and the Sequence Listing are incorporated herein by reference.

EXAMPLES

20 The following materials and methods were used in the Examples.

Strains, plasmids, bait cDNAs, and general microbiological techniques

Basic yeast strains (HF7c, Y187,) bait (pGBT9) and fish (pACT2) plasmids used in this work were purchased from Clontech (Palo Alto, CA). cDNAs encoding rat
25 Kv4.3, Kv4.2, and Kv1.1, were provided by Wyeth-Ayerst Research (865 Ridge Rd., Monmouth Junction, NJ 08852) Standard yeast media including synthetic complete medium lacking L-leucine, L-tryptophan, and L-histidine were prepared and yeast genetic manipulations were performed as described (Sherman (1991) *Meth. Enzymol.* 194:3-21). Yeast transformations were performed using standard protocols (Gietz *et al.*
30 (1992) *Nucleic Acids Res.* 20:1425; Ito

et al (1983) *J. Bacteriol.* 153:163-168). Plasmid DNAs were isolated from yeast strains by a standard method (Hoffman and Winston (1987) *Gene* 57:267-272).

Bait and Yeast Strain Construction

5 The first 180 amino acids of rKv4.3 (described in Serdio P. *et al.* (1996) *J. Neurophys* 75:2174-2179) were amplified by PCR and cloned in frame into pGBT9 resulting in plasmid pFWA2, (hereinafter "bait"). This bait was transformed into the two-hybrid screening strain HF7c and tested for expression and self-activation. The bait was validated for expression by Western blotting. The rKv4.3 bait did not self-activate
10 in the presence of 10 mM 3-amino-1,2,3-Triazole (3-AT).

Library construction

 Rat mid brain tissue was provided by Wyeth-Ayerst Research (Monmouth Junction, NJ). Total cellular RNA was extracted from the tissues using standard
15 techniques (Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989)). mRNA was prepared using a Poly-A Spin mRNA Isolation Kit from New England Biolabs (Beverly, MA). cDNA from the mRNA sample was synthesized using a cDNA Synthesis Kit from Stratagene (La
20 Jolla, CA) and ligated into pACT2's EcoRI and XhoI sites, giving rise to a two-hybrid library.

Two-Hybrid Screening

 Two-hybrid screens were carried out essentially as described in Bartel, P. *et al.*
25 (1993) "Using the Two-Hybrid System to Detect Polypeptide-Polypeptide Interactions" in *Cellular Interactions in Development: A Practical Approach*. Hartley, D.A. ed. Oxford University Press, Oxford, pp. 153-179, with a bait-library pair of rkv4.3 bait-rat mid brain library. A filter disk beta-galactosidase (beta-gal) assay was performed essentially as previously described (Brill *et al.* (1994) *Mol. Biol. Cell.* 5:297-312). Clones that were
30 positive for both reporter gene activity (His and beta-galactosidase) were scored and fish, plasmids were isolated from yeast, transformed into *E. coli* strain KC8, DNA

plasmids were purified and the resulting plasmids were sequenced by conventional methods (Sanger F. *et al.* (1977) *PNAS*, 74: 5463-67).

Specificity test

5 Positive interactor clones were subjected to a binding specificity test where they were exposed to a panel of related and unrelated baits by a mating scheme previously described (Finley R.L. Jr. *et al.* (1994) *PNAS*, 91(26):12980-12984). Briefly, positive fish plasmids were transformed into Y187 and the panel of baits were transformed into HF7c. Transformed fish and bait cells were streaked out as stripes on selective medium
10 plates, mated on YPAD plates, and tested for reporter gene activity.

Analysis

PCIP nucleotides were analyzed for nucleic acid hits by the BLASTN 1.4.8MP program (Altschul *et al.* (1990) Basic Local Alignment Search Tool. *J. Mol. Biol.* 215:
15 403-410). PCIP proteins were analyzed for polypeptide hits by the BLASTP 1.4.9MP program.

EXAMPLE 1: IDENTIFICATION OF RAT PCIP cDNAs

The Kv4.3 gene coding sequence (coding for the first 180 amino acids) was
20 amplified by PCR and cloned into pGBT9 creating a GAL4 DNA-binding domain-Kv4.3(1-180) gene fusion (plasmid pFWA2). HF7c was transformed with this construct. The resulting strain grew on synthetic complete medium lacking L-tryptophan but not on synthetic complete medium lacking L-tryptophan and L-histidine in the presence of 10mM 3-AT demonstrating that the {GAL4 DNA-binding domain}-
25 {vKv4.3(1-180)} gene fusion does not have intrinsic transcriptional activation activity higher than the threshold allowed by 10mM 3-AT .

In this example, a yeast two-hybrid assay was performed in which a plasmid containing a {GAL4 DNA-binding domain}-{rKv4.3(1-180)} gene fusion was introduced into the yeast two-hybrid screening strain HF7c described above. HF7c was
30 then transformed with the rat mid brain two-hybrid library. Approximately six million transformants were obtained and plated in selection medium. Colonies that grew in the

selection medium and expressed the beta-galactosidase reporter gene were further characterized and subjected to retransformation and specificity assays. The retransformation and specificity tests yielded three PCIP clones (rat 1v, 8t, and 9qm) that were able to bind to the Kv4.3 polypeptide.

5 The full length sequences for the rat 1v gene, and partial sequences for 8t and 9q genes were derived as follows. The partial rat PCIP sequences were used to prepare probes, which were then used to screen, for example, rat mid brain cDNA libraries. Positive clones were identified, amplified and sequenced using standard techniques, to obtain the full length sequence. Additionally, a rapid amplification of the existing rat
10 PCIP cDNA ends (using for example, 5' RACE, by Gibco, BRL) was used to complete the 5' end of the transcript.

EXAMPLE 2: IDENTIFICATION OF HUMAN 1v cDNA

To obtain the human 1v nucleic acid molecule, a cDNA library made from a
15 human hippocampus (Clontech, Palo Alto, CA) was screened under low stringency conditions as follows: Prehybridization for 4 hours at 42°C in Clontech Express Hyb solution, followed by overnight hybridization at 42°C. The probe used was a PCR-generated fragment including nucleotides 49-711 of the rat sequence labeled with ³²P dCTP. The filters were washed 6 times in 2XSSC/0.1% SDS at 55°C. The same
20 conditions were used for secondary screening of the positive isolates. Clones thus obtained were sequenced using an ABI automated DNA Sequencing system, and compared to the rat sequences shown in SEQ ID NO:3 as well as to known sequences from the GenBank database. The largest clone from the library screen was subsequently subcloned into pBS-KS+ (Stratagene, La Jolla, CA) for sequence verification. The 515
25 base pair clone was determined to represent the human homolog of the 1v gene, encompassing 211 base pairs of 5' UTR and a 304 base pair coding region. To generate the full-length cDNA, 3' RACE was used according to the manufacturers instructions (Clontech Advantage PCR kit).

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EXAMPLE 3: ISOLATION AND CHARACTERIZATION OF 1V SPLICE VARIANTS

The mouse 1v shown in SEQ ID NO:5 and the rat 1vl splice variant shown in SEQ ID NO:7 was isolated using a two-hybrid assay as described in Example 1. The mouse 1vl splice variant shown in SEQ ID NO: 7 was isolated by screening a mouse brain cDNA library, and the rat 1vn splice variant shown in SEQ ID NO:11 was isolated by BLAST searching.

EXAMPLE 4: ISOLATION AND IDENTIFICATION OF 9Q AND OTHER PCIPs

Rat 9ql (SEQ ID NO: 15) was isolated by database mining, rat 9qm (SEQ ID NO: 21) was isolated by a two-hybrid assay, and rat 9qc (SEQ ID NO:27) was identified by database mining. Human 9ql (SEQ ID NO: 13), and human 9qs (SEQ ID NO: 23) were identified as described in Example 2. Mouse 9ql (SEQ ID NO:17), monkey 9qs (SEQ ID NO:25), human p193 (SEQ ID NO:39), rat p19 (SEQ ID NO:33), and mouse p19 (SEQ ID NO:35) were identified by database mining. Rat 8t (SEQ ID NO:29) was identified using a two-hybrid assay. The sequence of W28559 (SEQ ID NO:37) was identified by database mining and sequencing of the identified EST with Genbank Accession Number AI352454. The protein sequence was found to contain a 41 amino acid region with strong homology to 1v, 9ql, and p19 (see alignment in Figure 25). However, downstream of this homologous region the sequence diverges from that of the PCIP family. This sequence could represent a gene which possesses a 41 amino acid domain with homology to a similar domain found in the PCIP family members.

The human genomic 9q sequence (SEQ ID NOs:46 and 47) was isolated by screening a BAC genomic DNA library (Reasearch Genetics) using primers which were designed based on the sequence of the human 9qm cDNA. Two positive clones were identified (448O2 and 721I17) and sequenced.

**EXAMPLE 5: EXPRESSION OF 1V, 8T, AND 9Q mRNA IN RAT
TISSUES**

Rat and mouse multiple tissue Northern blots (Clontech) were probed with a [32P]-labeled cDNA probe directed at the 5'-untranslated and 5'-coding region of the rat 1v sequence (nucleotides 35-124; SEQ ID NO:3) (this probe is specific for rat 1v and rat 1vl), the 5' coding region of the 8t sequence (nucleotides 1-88; SEQ ID NO:29) (this probe is specific for 8t), or the 5' end of the rat 9qm sequence (nucleotides 1-195; SEQ ID NO:21) (this probe is specific for all 9q isoforms, besides 8t). Blots were hybridized using standard techniques. Northern blots hybridized with the rat 1v probe revealed a single band at 2.3kb only in the lane containing brain RNA, suggesting that 1v expression is brain specific. Northern blots probed with the rat 8t probe revealed a major band at 2.4kb. The rat 8t band was most intense in the lane containing heart RNA and there was also a weaker band in the lane containing brain RNA. Northern blots hybridized with the 9q cDNA probe revealed a major band at 2.5kb and a minor band at over 4kb with predominant expression in brain and heart. The minor band may represent incompletely spliced or processed 9q mRNA. The results from the northern blots further indicated that p19 is expressed predominantly in the heart.

EXAMPLE 6: EXPRESSION OF 1V, 8T, AND 9Q IN BRAIN

Expression of the rat 1v and 8t/9q genes in the brain was examined by *in situ* hybridization histochemistry (ISHH) using [35S]-labeled cRNA probes and a hybridization procedure identical to that described in Rhodes *et al.* (1996) J. Neurosci., 16:4846-4860. Templates for preparing the cRNA probes were generated by standard PCR methods. Briefly, oligonucleotide primers were designed to amplify a fragment of 3'- or 5'-untranslated region of the target cDNA and in addition, add the promoter recognition sequences for T7 and T3 polymerase. Thus, to generate a 300 nucleotide probe directed at the 3'-untranslated region of the 1v mRNA, we used the following primers:

5-TAATACGACTCACTATAGGGACTGGCCATCCTGCTCTCAG-3 (T7, forward, sense; SEQ ID NO:42)

5-ATTAACCCTCACTAAAGGGACACTACTGTTTAAGCTCAAG-3 (T3, reverse, antisense; SEQ ID NO:43). The underlined bases correspond to the T7 and T3 promoter sequences. To generate a probe directed at a 325 bp region of 3'-untranslated sequence shared by the 8t and 9q mRNAs, the following primers were used:

5 5-TAATACGACTCACTATAGGGCACCTCCCCTCCGGCTGTTC-3 (T7, forward, sense; SEQ ID NO:44)

5-ATTAACCCTCACTAAAGGGAGAGCAGCAGCATGGCAGGGT-3 (T3, reverse, antisense; SEQ ID NO:45).

Autoradiograms of rat brain tissue sections processed for ISHH localization of 1v or 8t/9q mRNA expression revealed that 1v mRNA is expressed widely in brain in a pattern consistent with labeling of neurons as opposed to glial or endothelial cells. 1v mRNA is highly expressed in cortical, hippocampal, and striatal interneurons, the reticular nucleus of the thalamus, the medial habenula, and in cerebellar granule cells. 1v mRNA is expressed at moderate levels in midbrain nuclei including the substantia nigra and superior colliculus, in several other thalamic nuclei, and in the medial septal and diagonal band nuclei of the basal forebrain.

Because the probe used to analyze the expression of 8t and 9q hybridizes to a region of the 3'-untranslated region that is identical in the 8t and 9q mRNAs, this probe generates a composite image that reveals that 8t/9q mRNA is expressed widely in brain in a pattern that partly overlaps with that for 1v as described above. However, 8t/9q mRNA is highly expressed in the striatum, hippocampal formation, cerebellar granule cells, and neocortex. 8t/9q mRNA is expressed at moderate levels in the midbrain, thalamus, and brainstem. In many of these areas, 8t/9q mRNA appears to be concentrated in interneurons in addition to principal cells, and in all regions 8t/9q expression appears to be concentrated in neurons as opposed to glial cells.

Single- and double-label immunohistochemistry revealed that the PCIP and Kv4 polypeptides are precisely colocalized in many of the cell types and brain regions where PCIP and Kv4 mRNAs are coexpressed. For example, 9qm colocalized with Kv4.2 in the somata and dendrites of hippocampal granule and pyramidal cells, neurons in the medial habenular nucleus and in cerebellar basket cells, while 1v colocalized with Kv4.3 in layer II neurons of posterior cingulate cortex, hippocampal interneurons, and in a

subset of cerebellar granule cells. Immunoprecipitation analyses indicated that 1v and 9qm are coassociated with Kv4 α -subunits in rat brain membranes.

5

**EXAMPLE 7: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS
IN COS AND CHO CELLS**

COS1 and CHO cells were transiently transfected with individual PCIPs (KChIP1, KChIP2, KChIP3) alone or together with Kv4.2 or Kv4.3 using the
10 lipofectamine plus procedure essentially as described by the manufacturer (Boehringer Mannheim). Forty-eight hours after the transfection, cells were washed, fixed, and processed for immunofluorescent visualization as described previously (Bekele-Arcuri *et al.* (1996) *Neuropharmacology*, 35:851-865). Affinity-purified rabbit polyclonal or mouse monoclonal antibodies to the Kv4 channel or the PCIP protein were used for
15 immunofluorescent detection of the target proteins.

When expressed alone, the PCIPs were diffusely distributed throughout the cytoplasm of COS-1 and CHO cells, as would be expected for cytoplasmic proteins. In contrast, when expressed alone, the Kv4.2 and Kv4.3 polypeptides were concentrated within the perinuclear ER and Golgi compartments, with some immunoreactivity
20 concentrated in the outer margins of the cell. When the PCIPs were coexpressed with Kv4 α -subunits, the characteristic diffuse PCIP distribution changed dramatically, such that the PCIPs precisely colocalized with the Kv4 α -subunits. This redistribution of the PCIPs did not occur when they were coexpressed with the Kv1.4 α -subunit, indicating that altered PCIP localization is not a consequence of overexpression and that these
25 PCIPs associate specifically with Kv4-family α -subunits.

To verify that the PCIP and Kv4 polypeptides are tightly associated and not simply colocalized in co-transfected cells, reciprocal immunoprecipitation analyses were performed using the PCIP and channel-specific antibodies described above. All three PCIP polypeptides coassociated with Kv4 α -subunits in cotransfected cells, as
30 evidenced by the ability of anti-Kv4.2 and anti-Kv4.3 antibodies to immunoprecipitate

the KChIP1, KChIP2, and KChIP3 proteins from lysates prepared from cotransfected cells, and by the ability of anti-PCIP antibodies to immunoprecipitate Kv4.2 and Kv4.3 α -subunits from these same lysates. The cells were lysed in buffer containing detergent and protease inhibitors, and prepared for immunoprecipitation reactions essentially as described previously (Nakahira *et al.* (1996) J. Biol. Chem., 271:7084-7089). Immunoprecipitations were performed as described in Nakahira *et al.* (1996) J. Biol. Chem., 271:7084-7089 and in Harlow E. and Lane, D., Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, c1988. The products resulting from the immunoprecipitation were size fractionated by SDS-PAGE and transferred to nitrocellulose filters using standard procedures.

To confirm that the cytoplasmic N-terminus of Kv4 channels is sufficient for the interaction with the PCIPs KChIP1 or KChIP2 were co-expressed with a Kv4.3 mutant (Kv4.3 Δ C) that lacks the entire 219 amino acid cytoplasmic C-terminal tail. In transiently transfected COS-1 cells, the Kv4.3 Δ C mutant was extensively trapped within the perinuclear ER and Golgi: little or no staining was observed at the outer margins of the cell. Nonetheless, KChIP1 and KChIP2 precisely colocalized with Kv4.3 Δ C in cotransfected cells, and moreover, Kv4.3 Δ C was efficiently coimmunoprecipitated by PCIP antibodies, indicating that the interaction of these PCIPs with Kv4 α -subunits does not require the cytoplasmic C-terminus of the channel.

EXAMPLE 8: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS IN NATIVE TISSUES

To determine whether PCIPs colocalize and co-associate with Kv4 subunits in native tissues, Kv4- and PCIP-specific antibodies were used for single and double-label immunohistochemical analyses and for reciprocal coimmunoprecipitation analyses of rat brain membranes. Immunohistochemical staining of rat brain sections indicated that KChIP1 and KChIP2 colocalize with Kv4.2 and Kv4.3 in a region and cell type-specific manner. For example, KChIP1 colocalized with Kv4.3 in hippocampal interneurons, cerebellar granule cells, and cerebellar glomeruli, a specialized synaptic arrangement between the dendrites of cerebellar basket and golgi cells and mossy fiber terminals.

KChIP2 colocalized with Kv4.3 and Kv4.2 in the dendrites of granule cells in the dentate gyrus, in the apical and basal dendrites of hippocampal and neocortical pyramidal cells, and in several subcortical structures including the striatum and superior colliculus. Co-immunoprecipitation analyses performed using synaptic membranes prepared from whole rat brain revealed that the PCIPs (KChIPs 1, 2, and 3) are tightly associated with Kv4.2 and Kv4.3 in brain K⁺ channel complexes. Anti-PCIP antibodies immunoprecipitated Kv4.2 and Kv4.3 from brain membranes, and anti-Kv4.2 and Kv4.3 antibodies immunoprecipitated the PCIPs. None of the PCIP polypeptides were immunoprecipitated by anti-Kv2.1 antibodies, indicating that the association of these PCIPs with brain Kv channels may be specific for Kv4 α -subunits. Taken together, these anatomical and biochemical analyses indicate that these PCIPs are integral components of native Kv4 channel complexes.

EXAMPLE 9: PCIPs ARE CALCIUM BINDING PROTEINS

To determine whether KChIPs 1, 2, and 3 bind Ca²⁺, GST-fusion proteins were generated for each PCIP and the ability of the GST-PCIP proteins, as well as the recombinant PCIP polypeptides enzymatically cleaved from GST, to bind ⁴⁵Ca²⁺ was examined using a filter overlay assay (described in, for example, Kobayashi *et al.* (1993) *Biochem. Biophys. Res. Commun.* 189(1):511-7). All three PCIP polypeptides, but not an unrelated GST-fusion protein, display strong ⁴⁵Ca²⁺ binding in this assay. Moreover, all three PCIP polypeptides display a Ca²⁺-dependent mobility shift on SDS-PAGE, indicating that like the other members of this family, KChIPs 1, 2 and 3 are in fact Ca²⁺-binding proteins (Kobayashi *et al.* (1993) *supra*; Buxbaum *et al.* (1996). *Neuron-specific calcium sensors (the NCS-1 subfamily)*. In: Celio MR (ed) *Guidebook to the calcium-binding proteins*. Oxford University Press, New York, pp94-98; Buxbaum J.D., *et al.* (1998) *Nature Med.* 4(10):1177-81.

**EXAMPLE 10: ELECTROPHYSIOLOGICAL
CHARACTERIZATION OF PCIPs**

Because PCIPs, *e.g.*, KChIP1 (1v), KChIP2 (9ql), and KChIP3 (p19), colocalize and coassociate with Kv4 α -subunits in brain, another critical question was to determine whether these PCIPs alter the conductance properties of Kv4 channels. To address this issue, Kv4.2 and Kv4.3 were expressed alone and in combination with individual PCIPs. CHO cells were transiently-transfected with cDNA using the DOTAP lipofection method as described by the manufacturer (Boehringer Mannheim, Inc.). Transfected cells were identified by cotransfecting enhanced GFP along with the genes of interest and subsequently determining if the cells contained green GFP fluorescence. Currents in CHO cells were measured using the patch-clamp technique (Hamill *et al.* 1981. Pfluegers Arch. 391: 85-100).

Transient transfection of the rat Kv4.2 α -subunit in CHO cells resulted in expression of a typical A-type K⁺ conductance. Coexpression of Kv4.2 with KChIP1 revealed several dramatic effects of KChIP1 on the channel (Figure 41 and Table 1). First, the amplitude of the Kv4.2 current increased approximately 7.5 fold in the presence of KChIP1 (amplitude of Kv4.2 alone = 0.60 +/- 0.096 nA/cell; Kv4.2 + KChIP1 = 4.5 +/- 0.55 nA/cell). When converted into current density by correcting for cell capacitance, a measure of cell surface membrane area, the Kv4.2 current density increased 12 fold with coexpression of KChIP1 (Kv4.2 alone = 25.5 +/- 3.2 pA/pF; Kv4.2 + KChIP1 = 306.9 +/- 57.9 pA/pF), indicating that KChIPs promote and/or stabilize Kv4.2 surface expression. Together with this increase in current density, a dramatic leftward shift in the threshold for activation of Kv4.2 currents was observed in cells expressing Kv4.2 and KChIP1 (activation V_{1/2} for Kv4.2 alone = 20.8 +/- 7.0mV, Kv4.2 + KChIP1 = -12.1 +/- 1.4 mV). Finally, the kinetics of Kv4.2 inactivation slowed considerably when Kv4.2 was coexpressed with KChIP1 (inactivation time constant of Kv4.2 alone = 28.2 +/- 2.6 ms; Kv4.2 + KChIP1 = 104.1 +/- 10.4 ms), while channels recovered from inactivation much more rapidly in cells expressing both Kv4.2 and KChIP1 (recovery tau = 53.6 +/- 7.6 ms) versus cells expressing Kv4.2 alone (recovery tau = 272.2 +/- 26.1 ms).

KChIPs1, 2 and 3 have distinct N-termini but share considerable amino acid identity within the C-terminal "core" domain. Despite their distinct N-termini, the effects of KChIP2 and KChIP3 on Kv4.2 current density and kinetics were strikingly similar to those produced by KChIP1 (Table1). Thus to confirm that the conserved C-terminal core domain, which contains all three EF-hands, is sufficient to modulate Kv4 current density and kinetics, N-terminal truncation mutants of KChIP1 and KChIP2 were prepared. The KChIP1 Δ N2-31 and KChIP2 Δ N2-67 mutants truncated KChIP1 and KChIP2, respectively, to the C-terminal 185 amino acid core sequence. Coexpression of KChIP1 Δ N2-31 or KChIP2 Δ N2-67 with Kv4.2 in CHO cells produced changes in Kv4.2 current density and kinetics that were indistinguishable from the effects produced by full-length KChIP1 or KChIP2 (Table1).

To investigate whether the modulatory effects of these KChIPs are specific for Kv4 channels, KChIP1 was coexpressed with Kv1.4 and Kv2.1 in *Xenopus* oocytes. *Xenopus* oocytes were injected with 1-3 ng/oocyte of cRNA which was prepared using standard in vitro transcription techniques (Sambrook *et al.* 1989. Molecular Cloning: a laboratory manual, Cold Spring Harbor Press). Currents in oocytes were measured with a two-electrode voltage clamp. KChIP1 did not appear to have any effect on Kv1.4 or Kv2.1 currents (Table2), indicating that these functional effects may be specific for Kv4 channels. As a final control for the KChIP effects and to verify that the KChIPs' effects on Kv4 currents are independent of expression system, the above kinetic analyses were repeated after expressing Kv4.3 and KChIP mRNAs in *Xenopus* oocytes. The effects KChIP1 on for Kv4.3 in the oocyte system were strikingly similar to those on Kv4.2 in CHO cells (Table1).

Since these KChIPs bind Ca²⁺, another important question is to determine whether the effects of KChIP1 on Kv4.2 currents are Ca²⁺-dependent. This question was addressed indirectly by introducing point mutations within each of KChIP1's EF-hand domains: one mutant has point mutations in the first two EF hands (D₁₉₉ to A, G₁₀₄ to A, D₁₃₅ to A, and G₁₄₀ to A) and the other one has point mutations in all three EF hands (D₁₉₉ to A, G₁₀₄ to A, D₁₃₅ to A, G₁₄₀ to A, D₁₈₃ to A, and G₁₈₈ to A). These mutations substituted alanine for the two most highly conserved amino acids within the EF-hand consensus (Figure 25; Linse, S. and Forsen, S. (1995) Determinants that govern high-

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affinity Calcium binding. In Means, S. (Ed.) Advances in second messenger and phosphoprotein research. New York, Ravens Press., 30:89-150). Coexpression of this KChIP1 triple EF-hand mutant with Kv4.2 or Kv4.3 in COS cells indicated that this mutant colocalizes and is efficiently coimmunoprecipitated with Kv4 α -subunits in

5 COS-1 cells. However, these EF-hand point mutations completely eliminated the effects of KChIP1 on Kv4.2 kinetics (Table1). Taken together, these results indicate that the binding interaction between KChIP1 and Kv4.2 is Ca^{2+} independent, while modulation of Kv4.2 kinetics by KChIP1 is either Ca^{2+} -dependent or sensitive to structural changes induced by point mutations within the EF-hand domains.

TABLE 1

Functional effect of KchIPs on Kv4 channels

Current Parameter	rKv4.2 + vector	rKv4.2 + KchIP1	rKv4.2 + KchIP1 Δ N2-31	rKv4.2 + KchIP2	rKv4.2 + KchIP2 Δ N2-67	rKv4.2 + KchIP3	rKv4.3	rKv4.3 + KchIP1
Peak Current	0.60*	4.5*	6.0*	3.3*	5.8*	3.5*	7.7 μ A	18.1 μ A*
(nA/cell at 50 mV)	\pm 0.096	\pm 0.055	\pm 1.1	\pm 0.45	\pm 1.1	\pm 0.99	\pm 2.6	\pm 3.8
Peak Current Density	25.5	306.9*	407.2*	196.6*	202.6*	161.7*	---	---
(pA/pF at 50 mV)	\pm 3.2	\pm 57.9	\pm 104.8	\pm 26.6	\pm 27.5	\pm 21.8		
Inactivation time constant	28.2	104.1	129.2	95.1*	109.5*	67.2*	56.3	135.0
(ms, at 50 mV)	\pm 2.6	\pm 10.4	\pm 14.2	\pm 8.3	\pm 9.6	\pm 14.1	\pm 6.6	\pm 15.1
Recovery from Inactivation Time constant	272.2	53.6*	98.1*	49.5*	36.1*	126.1*	327.0	34.5*

* Significantly different from control.

TABLE 2

Functional effects of KChIPs on other Kv channels

Current Parameter	Oocytes		Oocytes	
	HKv1.4	hKv1.4 + 1v	HKv2.1	HKv2.1 + 1v
Peak Current	8.3	6.5	3.7	2.9
(μ A/cell at 50 MV)	± 2.0	± 0.64	± 0.48	± 0.37
Inactivation time constant	53.2	58.2	1.9 s	1.7 s
(ms, at 50 mV)	± 2.8	± 6.6	± 0.079	0.078
Recovery from Inactivation time constant (sec, at -80 mV)	1.9	1.6	7.6	7.7
Activation $V_{1/2}$ (mV)	-21.0	-20.9	12.0	12.4
Steady-state Inactivation $V_{1/2}$ (mV)	-48.1	-47.5	-25.3	-23.9

5 **EXAMPLE 11: EFFECTS OF KChIP1 ON SURFACE EXPRESSION OF KV4- α SUBUNITS IN COS-1 CELLS**

To examine the ability of KChIP1 to enhance the surface expression of Kv4 channels, the ability of KChIP1 to promote the formation of surface co-clusters of Kv4 channels and PSD-95 was monitored. PSD-95 is used to facilitate the visualization of
10 the complex.

To facilitate the interaction between Kv4.3 and PSD-95, a chimeric Kv4.3 subunit (Kv4.3ch) was generated in which the C-terminal 10 amino acids from rKv1.4

(SNAKAVETDV, SEQ ID NO:73) were appended to the C-terminus of Kv4.3. The C-terminal 10 amino acids from rKv1.4 were used because they associate with PSD-95 and confer the ability to associate with PSD-95 to the Kv4.3 protein when fused to the Kv4.3 C-terminus. Expression of Kv4.3ch in COS-1 cells revealed that the Kv4.3ch

5 polypeptide was trapped in the perinuclear cytoplasm, with minimal detectable Kv4.3ch immunoreactivity at the outer margins of the cell. When Kv4.3ch was co-expressed with PSD-95, PSD-95 became trapped in the perinuclear cytoplasm and co-localized with Kv4.3ch. However, when KCHIP1 was co-expressed with Kv4.3ch and PSD-95, large plaque-like surface co-clusters of Kv4.3ch, KCHIP1 and PSD-95 were observed.

10 Triple-label immunofluorescence confirmed that these surface clusters contain all three polypeptides, and reciprocal co-immunoprecipitation analyses indicated that the three polypeptides are co-associated in these surface clusters. Control experiments indicated that KCHIP1 does not interact with PSD-95 alone, and does not co-localize with Kv1.4 and PSD-95 in surface clusters. Taken together, these data indicate that KCHIP1 may

15 promote the transit of the Kv4.3 subunits to the cell surface.

EXAMPLE 12: CHARACTERIZATION OF THE PCIP PROTEINS

In this example, the amino acid sequences of the PCIP proteins were compared to amino acid sequences of known proteins and various motifs were identified.

20 The 1v polypeptide, the amino acid sequence of which is shown in SEQ ID NO:3 is a novel polypeptide which includes 216 amino acid residues. Domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by sequence alignment (see

25 Figure 21).

The 8t polypeptide, the amino acid sequence of which is shown in SEQ ID NO:30 is a novel polypeptide which includes 225 amino acid residues. Calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by

30 sequence alignment (see Figure 21).

The 9q polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

5 The p19 polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

10 A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of rat 1vl revealed that the rat 1vl is similar to the rat cDNA clone RMUAH89 (Accession Number AA849706). The rat 1 vl nucleic acid molecule is 98% identical to the rat cDNA clone RMUAH89 (Accession Number AA849706) over nucleotides 1063 to 1488.

15 A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of human 9ql revealed that the human 9ql is similar to the human cDNA clone 1309405 (Accession Number AA757119). The human 9 ql nucleic acid molecule is 98% identical to the human cDNA clone 1309405 (Accession Number AA757119) over nucleotides 937 to 1405.

20 A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of mouse P19 revealed that the mouse P19 is similar to the *Mus musculus* cDNA clone MNCb-7005 (Accession Number AU035979). The mouse P19 nucleic acid molecule is 98% identical to the *Mus musculus* cDNA clone MNCb-7005 (Accession Number AU035979) over nucleotides 1 to 583.

25 **EXAMPLE 13: EXPRESSION OF RECOMBINANT PCIP PROTEINS IN BACTERIAL CELLS**

30 In this example, PCIP is expressed as a recombinant glutathione-S-transferase (GST) fusion polypeptide in *E. coli* and the fusion polypeptide is isolated and characterized. Specifically, PCIP is fused to GST and this fusion polypeptide is expressed in *E. coli*, *e.g.*, strain BI21. Expression of the GST-PCIP fusion protein in BI21 is induced with IPTG. The recombinant fusion polypeptide is purified from crude

bacterial lysates of the induced BI21 strain by affinity chromatography on glutathione beads. Using polyacrylamide gel electrophoretic analysis of the polypeptide purified from the bacterial lysates, the molecular weight of the resultant fusion polypeptide is determined.

5 Rat 1v and 9ql were cloned into pGEX-6p-2 (Pharmacia). The resulting recombinant fusion proteins were expressed in *E. coli* cells and purified following art known methods (described in, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). The identities of the purified proteins were verified by western blot analysis using antibodies raised against peptide epitopes of
10 rat 1v and 9ql.

EXAMPLE 14: EXPRESSION OF RECOMBINANT PCIP PROTEINS IN COS CELLS

To express the PCIP gene in COS cells, the pcDNA/Amp vector by Invitrogen
15 Corporation (San Diego, CA) is used. This vector contains an SV40 origin of replication, an ampicillin resistance gene, an *E. coli* replication origin, a CMV promoter followed by a polylinker region, and an SV40 intron and polyadenylation site. A DNA fragment encoding the entire PCIP protein and an HA tag (Wilson *et al.* (1984) *Cell* 37:767) or a FLAG tag fused in-frame to its 3' end of the fragment is cloned into the
20 polylinker region of the vector, thereby placing the expression of the recombinant protein under the control of the CMV promoter.

To construct the plasmid, the PCIP DNA sequence is amplified by PCR using two primers. The 5' primer contains the restriction site of interest followed by approximately twenty nucleotides of the PCIP coding sequence starting from the
25 initiation codon; the 3' end sequence contains complementary sequences to the other restriction site of interest, a translation stop codon, the HA tag or FLAG tag and the last 20 nucleotides of the PCIP coding sequence. The PCR amplified fragment and the pCDNA/Amp vector are digested with the appropriate restriction enzymes and the vector is dephosphorylated using the CIAP enzyme (New England Biolabs, Beverly,
30 MA). Preferably the two restriction sites chosen are different so that the PCIP gene is inserted in the correct orientation. The ligation mixture is transformed into *E. coli* cells

(strains HB101, DH5a, SURE, available from Stratagene Cloning Systems, La Jolla, CA, can be used), the transformed culture is plated on ampicillin media plates, and resistant colonies are selected. Plasmid DNA is isolated from transformants and examined by restriction analysis for the presence of the correct fragment.

5 COS cells are subsequently transfected with the PCIP-pcDNA/Amp plasmid DNA using the calcium phosphate or calcium chloride co-precipitation methods, DEAE-dextran-mediated transfection, lipofection, or electroporation. Other suitable methods for transfecting host cells can be found in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, 10 Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989. The expression of the PCIP polypeptide is detected by radiolabelling (^{35}S -methionine or ^{35}S -cysteine available from NEN, Boston, MA, can be used) and immunoprecipitation (Harlow, E. and Lane, D. *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988) using an HA specific monoclonal antibody. Briefly, the 15 cells are labelled for 8 hours with ^{35}S -methionine (or ^{35}S -cysteine). The culture media are then collected and the cells are lysed using detergents (RIPA buffer, 150 mM NaCl, 1% NP-40, 0.1% SDS, 0.5% DOC, 50 mM Tris, pH 7.5). Both the cell lysate and the culture media are precipitated with an HA specific monoclonal antibody. Precipitated polypeptides are then analyzed by SDS-PAGE.

20 Alternatively, DNA containing the PCIP coding sequence is cloned directly into the polylinker of the pCDNA/Amp vector using the appropriate restriction sites. The resulting plasmid is transfected into COS cells in the manner described above, and the expression of the PCIP polypeptide is detected by radiolabelling and immunoprecipitation using a PCIP specific monoclonal antibody.

25 Rat 1v was cloned into the mammalian expression vector pRBG4. Transfections into COS cells were performed using LipofectAmine Plus (Gibco BRL) following the manufacturer's instructions. The expressed 1v protein was detected by immunocytochemistry and/or western blot analysis using antibodies raised against 1v in rabbits or mice.

**EXAMPLE 15: IDENTIFICATION AND CHARACTERIZATION OF
HUMAN FULL LENGTH P19**

The human full length p19 sequence was identified using RACE PCR. The sequence of p19 (also referred to as KChIP3) is shown in Figure 16. The amino acid
5 sequence of human p19 is 92% identical to the mouse p19 gene (SEQ ID NO:35).

TBLASTN searches using the protein sequence of human p19 revealed that human p19 is homologous to two sequences, Calsenilin (described in (1998) *Nature Medicine* 4: 1177-1181) and DREAM, a Ca²⁺-dependent regulator of prodynorphin and c-fos transcription (described in Carrion *et al.* (1999) *Nature* 398: 80-84). Human p19 is
10 100% identical at the nucleotide level to Calsenilin (but extends 3' to the published sequence) and 99% identical at the nucleotide level to DREAM.

The ability of p19 (as well as other PCIP family members) to co-localize with presenilin and act as transcription factors is determined using art known techniques such as northern blots, *in situ* hybridization, β -gal assays, DNA mobility assays (described in,
15 for example, Carrion *et al.* (1999) *Nature* 398:80) and DNA mobility supershift assays, using antibodies specific for KchIPs.

Other assays suitable for evaluating the association of PCIP family members with presenilins is co-immunoprecipitation (described in, for example, Buxbaum *et al.* (1998) *Nature Medicine* 4:1177).

20

**EXAMPLE 16: IDENTIFICATION AND CHARACTERIZATION OF
MONKEY KChIP4**

In this example, the identification and characterization of the genes encoding monkey KChIP4a (jlkbd352e01t1) and alternatively spliced monkey KChIP4b
25 (jlkbb231c04t1), KChIP4c (jlkxa053c02), and KChIP4d (jlkx015b10) is described. TBLASTN searches in proprietary databases with the sequence of the known PCIP family members, lead to the identification of four clones jlkbb231c04t1, jlkbd352e01t1, jlkxa053c02, and jlkx015b10. The four monkey clones were obtained and sequenced.

The sequences of proprietary monkey clones jlkbb231c04t1 and jlkbd352e01t1
30 were found to correspond to alternately spliced variants of an additional PCIP family member, referred to herein as KChIP4. Clone jlkbb231c04t1 contains a 822bp deletion

relative to jlkbd352e01t1 (presumably due to splicing out of an exon), resulting in the loss of the final EF hand domain. In clone jlkbd352e01t1, the final EF hand domain is preserved, and the C-terminus is highly homologous to that of PCIP family members 1v, 9ql, and p19. Overall identity in the homologous C-termini among KChIP4. 1v, 9ql, and p19 ranged from 71%-80% at the amino acid level (alignments were performed using the CLUSTALW).

Monkey KChIP4c and KChIP4d were discovered by BLASTN search using monkey KChIP4a as a query for searching a proprietary database.

The nucleotide sequence of the monkey KChIP4a cDNA and the predicted amino acid sequence of the KChIP4a polypeptide are shown in Figure 23 and in SEQ ID NOs:48 and 49, respectively.

The nucleotide sequence of the monkey KChIP4b cDNA and the predicted amino acid sequence of the KChIP4b polypeptide are shown in Figure 24 and in SEQ ID NOs:50 and 51, respectively.

The nucleotide sequence of the monkey KChIP4c cDNA and the predicted amino acid sequence of the KChIP4c polypeptide are shown in Figure 35 and in SEQ ID NOs:69 and 70, respectively.

The nucleotide sequence of the monkey KChIP4d cDNA and the predicted amino acid sequence of the KChIP4d polypeptide are shown in Figure 36 and in SEQ ID NOs:71 and 72, respectively.

Figure 37 depicts an alignment of the protein sequences of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Rat KChIP4 is predominantly expressed in the brain, and weakly in the kidney, but not in the heart, brain, spleen, lung, liver, skeletal muscle or testes, as indicated by northern blot experiments in which a northern blot purchased from Clontech was probed with a DNA fragment from the 3'-untranslated region of rat KChIP4.

EXAMPLE 17: IDENTIFICATION AND CHARACTERIZATION OF HUMAN AND RAT 33b07

In this example, the identification and characterization of the genes encoding rat and human 33b07 is described. Partial rat 33b07 (clone name 9o) was isolated as a

positive clone from the yeast two-hybrid screen described above, using rKv4.3N as bait. The full length rat 33b07 clone was identified by mining of proprietary databases.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ
5 ID NOs:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in length.

Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays. In contrast, rat 33b07 does not bind rKv1.1N, indicating that the
10 rat 33b07-Kv4N interaction is specific.

Rat 33b07 is expressed predominantly in the brain as determined by northern blot analysis.

The human 33b07 ortholog (clone 106d5) was also identified by mining of proprietary databases. The nucleotide sequence of the full length human 33b07 cDNA
15 and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in SEQ ID NOs:54 and 55, respectively. The human 33b07 cDNA encodes a protein having a molecular weight of approximately 45.1 kD and which is 414 amino acid residues in length.

Human 33b07 is 99% identical to the human KIAA0721 protein (GenBank
20 Accession Number: AB018264) at the amino acid level. However, GenBank Accession Number: AB018264 does not have a functional annotation. Human 33b07 is also homologous to Testes-specific (Y-encoded) proteins (TSP(Y)s), SET, and Nucleosome Assembly Proteins (NAPs). The human 33b07 is 38% identical to human SET protein (GenBank Accession Number Q01105=U51924) over amino acids 204 to 337 and 46%
25 identical over amino acids 334 to 387.

Human SET is also called HLA-DR associated protein II (PHAPII) (Hoppe-Seyler (1994) *Biol. Chem.* 375:113-126) and in some cases is associated with acute undifferentiated leukemia (AUL) as a result of a translocation event resulting in the formation of a SET-CAN fusion gene (Von Lindern M. *et al.* (1992) *Mol. Cell. Biol.*
30 12:3346-3355). An alternative spliced form of SET is also called Template Activating Factor-I alpha (TAF). TAF is found to be associated with myeloid leukemogenesis

(Nagata K. *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A.* 92 (10), 4279-4283). Human SET is also a potent protein inhibitor of phosphatase 2A (Adachi Y. *et al.* (1994) *J. Biol. Chem.* 269:2258-2262). NAPs may be involved in modulating chromatin formation and contribute to regulation of cell proliferation (Simon H.U. *et al.* (1994) *Biochem. J.* 297, 5 389-397).

Thus, due to its homology to the above identified proteins, 33b07 may function as a protein inhibitor of phosphatase, an oncogene, and/or a chromatin modulator. The homology of 33b07 to SET, a protein phosphatase inhibitor, is of particular interest. Many channels, in particular the Kv4 channels (with which 33b07 is associated), are 10 known to be regulated by phosphorylation by PKC and PKA ((1998) *J. Neuroscience* 18(10): 3521-3528; *Am J Physiol* 273: H1775-86 (1997)). Thus, 33b07 may modulate Kv4 activity by regulating the phosphorylation status of the potassium channel.

15 **EXAMPLE 18: IDENTIFICATION AND CHARACTERIZATION OF RAT 1p**

In this example, the identification and characterization of the gene encoding rat 1p is described. Partial rat 1p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted 20 amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length.

Rat 1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 1p does not bind rKv1.1N, indicating that the 1p-Kv4N 25 interaction is specific.

Rat 1p is predominantly expressed in the brain as determined by northern blot analysis.

A BLASTP 1.4 search, using a score of 100 and a word length of 3 (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the amino acid sequences of rat 1p revealed that rat 30 1p is similar to the human Restin (GenBank Accession Number P30622; also named cytoplasmic linker protein-170 alpha-2 (CLIP-170), M97501)). The rat 1p protein is

58% identical to the human Restin over amino acid residues 105 to 182, 55% identical to the human Restin over amino acid residues 115 to 186, 22% identical to the human Restin over amino acid residues 173 to 246, 22% identical to the human Restin over amino acid residues 169 to 218, and 58% identical to the human Restin over amino acid residues 217 to 228.

Restin is also named Reed-Sternberg intermediate filament associated protein. Reed-Sternberg cells are the tumoral cells diagnostic for Hodgkin's disease. It is suggested that Restin overexpression may be a contributing factor in the progression of Hodgkin's disease (Bilbe G. *et al.* (1992) *EMBO J.* 11: 2103-13) and Restin appears to be an intermediate filament associated protein that links endocytic vesicles to microtubules (Pierre P, *et al.* (1992) *Cell* 70 (6), 887-900).

The cytoskeleton regulates the activity of potassium channels (see, for example, Honore E, *et al.* (1992) *EMBO J.* 11:2465-2471 and Levin G, *et al.* (1996) *J. Biol. Chem.* 271:29321-29328), as well as the activity of other channels, *e.g.*, Ca⁺⁺ channels (Johnson B.D. *et al.* (1993) *Neuron* 10:797-804); or Na⁺ channels (Fukuda J. *et al.* (1981) *Nature* 294:82-85).

Accordingly, based on its homology to the Restin protein, the rat 1p protein may be associated with the cytoskeleton and may modulate the activity of potassium channels, *e.g.*, Kv4, via its association to the cytoskeleton.

EXAMPLE 19: IDENTIFICATION AND CHARACTERIZATION OF RAT 7s

In this example, the identification and characterization of the gene encoding rat 7s is described. Partial rat 7s was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Rat 7s is the rat ortholog of the human vacuolar H(+)-ATPase catalytic subunit A (Accession Number P38606 and B46091) described in, for example, van Hille B. *et al.* (1993) *J. Biol. Chem.* 268 (10), 7075-7080.

The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 270 amino acid residues in length.

Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays. In contrast, 7s does not bind rKv1.1N, indicating that the 7s-Kv4N interaction is specific.

Rat 7s is expressed at significantly higher levels in the brain and the kidney than
5 in the lung, liver, heart, testes, and skeletal muscle, as determined by northern blot analysis.

EXAMPLE 20: IDENTIFICATION AND CHARACTERIZATION OF RAT 29x AND 25r

10 In this example, the identification and characterization of the gene encoding rat 29x is described. Rat 29x was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Rat 25r is a splice variant of 29x. They differ in the 5' untranslated region, but are identical in the coding region and at the amino acid level.

15 The nucleotide sequence of the rat 29x cDNA and the predicted amino acid sequence of the rat 29x polypeptide are shown in Figure 30 and in SEQ ID NOs:60 and 61, respectively. The rat 29x cDNA encodes a protein having a molecular weight of approximately 40.4 kD and which is 351 amino acid residues in length.

The nucleotide sequence of the rat 25r cDNA is shown in Figure 31 and in SEQ
20 ID NO:62. The rat 25r cDNA encodes a protein having a molecular weight of approximately 40.4 kD and which is 351 amino acid residues in length.

Rat 29x is expressed in the spleen, lung, kidney, heart, brain, testes, skeletal muscle and liver, with the highest level of expression being in the spleen and the lowest being in the liver.

25 Rat 29x binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 29x does not bind rKv1.1N, indicating that the 29x-Kv4N interaction is specific.

Rat 29x is identical at the amino acid level to rat SOCS-1 (Suppressor Of Cytokine Signaling) described in Starr R. *et al.* (1997) *Nature* 387: 917-921; to JAB described in Endo T.A. *et al.* (1997) *Nature* 387: 921-924; and to SSI-1 (STAT-induced
30 STAT inhibitor-1) described in Naka T. *et al.* (1997) *Nature* 387:924-928. These

proteins are characterized in that they have an SH2 domain, bind to and inhibit JAK kinase, and, as a result, regulate cytokine signaling.

As used herein, the term "SH2 domain", also referred to a Src Homology 2 domain, includes a protein domain of about 100 amino acids in length which is involved in binding of phosphotyrosine residues, *e.g.*, phosphotyrosine residues in other proteins. The target site is called an SH2-binding site. The SH2 domain has a conserved 3D structure consisting of two alpha helices and six to seven beta-strands. The core of the SH2 domain is formed by a continuous beta-meander composed of two connected beta-sheets (Kuriyan J. *et al.* (1997) *Curr. Opin. Struct. Biol.* 3:828-837). SH2 domains function as regulatory modules of intracellular signaling cascades by interacting with high affinity to phosphotyrosine-containing target peptides in a sequence-specific and strictly phosphorylation-dependent manner (Pawson T. (1995) *Nature* 373:573-580). Some proteins contain multiple SH2 domains, which increases their affinity for binding to phosphoproteins or confers the ability to bind to different phosphoproteins. Rat 29x contains an SH2 domain at amino acid residues 219-308 of SEQ ID NO:61.

Tyrosine phosphorylation regulates potassium channel activity (Prevarskaya N.B. *et al.* (1995) *J. Biol. Chem.* 270:24292-24299). JAK kinase phosphorylates proteins at tyrosines and is implicated in the regulation of channel activity (Prevarskaya N.B. *et al. supra*). Accordingly, based on its homology to SOCS-1, JAB, and SSI-1, rat 29x may modulate the activity of potassium channels, *e.g.*, Kv4, by modulating JAK kinase activity.

EXAMPLE 21: IDENTIFICATION AND CHARACTERIZATION OF RAT 5p

In this example, the identification and characterization of the gene encoding rat 5p is described. Rat 5p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the rat 5pc DNA and the predicted amino acid sequence of the rat 5p polypeptide are shown in Figure 32 and in SEQ ID NOs:63 and 64, respectively. The rat 5p cDNA encodes a protein having a molecular weight of approximately 11.1 kD and which is 95 amino acid residues in length.

5 Rat 5p binds rKv4.3N and rKv4.2N with similar strength in yeast two-hybrid assays. In contrast, 5p does not bind rKv1.1N, indicating that the 5p-Kv4N interaction is specific.

Rat 5p is expressed in the spleen, lung, skeletal muscle, heart, kidney, brain, liver, and testes, as determined by northern blot analysis.

10 The rat 5p is identical to rat Calpactin I light chain or P10 (Accession Number P05943). P10 binds and induces the dimerization of annexin II (p36). P10 may function as a regulator of protein phosphorylation in that the p36 monomer is the preferred target of a tyrosine-specific kinase (Masiakowski P. *et al.* (1998) *Proc. Natl. Acad. Sci. U.S.A.* 85 (4): 1277-1281).

15 Tyrosine phosphorylation regulates the activity of potassium channels (Prevarskaya N.B. *et al. supra*). Thus, due to its identity to P10, rat 5p may modulate the activity of potassium channels, *e.g.*, Kv4, by modulating the activity of a tyrosine-specific kinase.

20 **EXAMPLE 22: IDENTIFICATION AND CHARACTERIZATION OF**
 RAT 7q

In this example, the identification and characterization of the gene encoding rat 7q is described. Rat 7q was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 7q was obtained by RACE PCR.

The nucleotide sequence of the rat 7q cDNA and the predicted amino acid sequence of the rat 7q polypeptide are shown in Figure 33 and in SEQ ID NOs:65 and 66, respectively. The rat 7q cDNA encodes a protein having a molecular weight of approximately 23.5 kD and which is 212 amino acid residues in length.

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Rat 7q binds rKv4.3N and rKv4.2N with same strength in yeast two-hybrid assays. In contrast, 7q does not bind rKv1.1N, indicating that the 7q-Kv4N interaction is specific.

Rat 7q is expressed in the heart, brain, spleen, lung, liver, skeletal muscle,
5 kidney, and testes, as determined by northern blot analysis.

Rat 7q is identical to RAB2 (rat RAS-related protein, Accession Number P05712) at the amino acid level. RAB2 appears to be involved in vesicular traffic and protein transport

(Touchot N. *et al.* (1987) *Proc. Natl. Acad. Sci. U.S.A.* 84 (23): 8210-8214).

10 Accordingly, based on its homology to RAB2, rat 7q may be involved in potassium channel, *e.g.*, Kv4, trafficking.

EXAMPLE 23: IDENTIFICATION AND CHARACTERIZATION OF

15 RAT 19r

In this example, the identification and characterization of the gene encoding rat 19r is described. Partial rat 19r was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 19r was obtained by RACE PCR.

20 The nucleotide sequence of the rat 19r cDNA and the predicted amino acid sequence of the rat 19r polypeptide are shown in Figure 34 and in SEQ ID NOs:67 and 68, respectively. The rat 19r cDNA encodes a protein having a molecular weight of approximately 31.9 kD and which is 271 amino acid residues in length.

Rat 19r is expressed in the heart, brain, spleen, lung, liver, skeletal muscle,
25 kidney, and testes, as determined by northern blot analysis.

Rat 19r binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 19r does not bind rKv1.1N, indicating that the 19r-Kv4N interaction is specific.

Rat 19r is identical to Rat phosphatidylinositol (PTDINS) transfer protein alpha
30 (PTDINSTP, Accession Number M25758 or P16446) described in Dickeson S.K. *et al.* (1989) *J. Biol. Chem.* 264:16557-16564. PTDINSTP is believed to be involved in

phospholipase C-beta (PLC-beta) signaling, phosphatidylinositol transfer protein (PtdIns-TP) synthesis, secretory vesicle formation, and enhancement of phosphatidylinositol 3-kinase (PtdIns 3-kinase) activity (Cunningham E. *et al.* (1995) *Curr. Biol.* 5 (7): 775-783; (1995) *Nature* 377 (6549): 544-547; and Panaretou C. *et al.* 5 (1997) *J. Biol. Chem.* 272 (4): 2477-2485).

Accordingly, based on its homology with PTDINSTP, rat 19r may modulate potassium channel, *e.g.*, Kv4, activity via the PLC-beta signaling pathway and/or the PtdIns 3-kinase signaling pathway. Rat p19r may also be involved in potassium channel, *e.g.*, Kv4, trafficking.

10

EXAMPLE 24: CHROMOSOMAL LOCALIZATION OF HUMAN 9q

In this example, the human PCIP 9q was chromosomally mapped using a radiation hybrid panel (Panel GB4). h9q mapped to a region of chromosome 10q that had been previously shown to contain a linkage with partial epilepsy, namely D10S192: 15 10q22-q24 (Ottman *et al.* (1995) *Nature Genetics* 10:56-60) (see Figure 43). Based on this observation, the present invention clearly demonstrates that the 9q family of proteins can serve as targets for developing anti-epilepsy drugs and as targets for medical intervention of epilepsy.

Furthermore, h9q mapped to a region of chromosome 10q that had been 20 previously shown to contain a linkage with IOSCA, namely D10S192 and D10S1265: 10q24- Nikali (Genomics 39:185-191 (1997)) (see Figures 42 and 43). Based on this observation, the present invention clearly demonstrates that the 9q family of proteins can serve as targets for developing anti-spinocerebellar ataxia drugs and as targets for medical intervention of spinocerebellar ataxia.

25

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following 30 claims.

What is claimed is:

1. An isolated nucleic acid molecule selected from the group consisting of:
 - 5 a) a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, 10 SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 15 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof;
 - b) a nucleic acid molecule comprising a fragment of at least 583 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, 20 SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 25 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof;
 - c) a nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence at least about 60% identical to the amino acid sequence 30 of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID

NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or
5 an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;

d) a nucleic acid molecule which encodes a fragment of a
10 polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID
15 NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or
20 PTA-316, wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID
25 NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316; and
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- e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, under stringent conditions.

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2. The isolated nucleic acid molecule of claim 1 which is selected from the group consisting of:

- 5 a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA
10 insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof; and
- 15 b) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ
20 ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

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3. The nucleic acid molecule of claim 1 further comprising vector nucleic acid sequences.

4. The nucleic acid molecule of claim 1 further comprising nucleic acid
30 sequences encoding a heterologous polypeptide.

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5. A host cell which contains the nucleic acid molecule of claim 1.
6. The host cell of claim 5 which is a mammalian host cell.
- 5 7. A non-human mammalian host cell containing the nucleic acid molecule of claim 1.
8. An isolated polypeptide selected from the group consisting of:
 - 10 a) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, 15 SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 20 98991, 98993, 98994, or PTA-316, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, 25 SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 30 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316 under stringent conditions; and

c) a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited

with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

5 d) a polypeptide comprising an amino acid sequence which is at least 60% identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

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9. The isolated polypeptide of claim 8 comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

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10. The polypeptide of claim 8 further comprising heterologous amino acid sequences.

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11. An antibody which selectively binds to a polypeptide of claim 8.

12. A method for producing a polypeptide selected from the group consisting of:

- 5 a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid
10 sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;
- 15 b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID
20 NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the fragment comprises at least 15
25 contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID
30 NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the

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plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316; and

- 5 c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or
10 SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the
15 polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or
20 SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316 under stringent conditions;
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comprising culturing the host cell of claim 5 under conditions in which the nucleic acid molecule is expressed.

13. A method for detecting the presence of a polypeptide of claim 8 in a sample comprising:

- a) contacting the sample with a compound which selectively binds to the polypeptide; and
- 5 b) determining whether the compound binds to the polypeptide in the sample to thereby detect the presence of a polypeptide of claim 8 in the sample.

14. The method of claim 13, wherein the compound which binds to the
10 polypeptide is an antibody.

15. A kit comprising a compound which selectively binds to a polypeptide of claim 8 and instructions for use.

15 16. A method for detecting the presence of a nucleic acid molecule in claim 1 in a sample comprising:

- a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and
- 20 b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a nucleic acid molecule of claim 1 in the sample.

17. The method of claim 16, wherein the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

25

18. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1 and instructions for use.

19. A method for identifying a compound which binds to a polypeptide of claim 8 comprising:

- a) contacting the polypeptide, or a cell expressing the polypeptide with a test compound; and
- 5 b) determining whether the polypeptide binds to the test compound.

20. The method of claim 19, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

- a) detection of binding by direct detection of test compound/polypeptide binding;
- 10 b) detection of binding using a competition binding assay; and
- c) detection of binding using an assay for PCIP activity.

21. A method for modulating the activity of a polypeptide of claim 8 comprising contacting the polypeptide or a cell expressing the polypeptide with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide.

22. A method for identifying a compound which modulates the activity of a polypeptide of claim 8 comprising:

- a) contacting a polypeptide of claim 8 with a test compound; and
- b) determining the effect of the test compound on the activity of the polypeptide to thereby identify a compound which modulates the activity of the polypeptide.

25

23. A method for identifying a compound capable of treating a disorder characterized by aberrant PCIP nucleic acid expression or PCIP protein activity comprising assaying the ability of the compound or agent to modulate the expression of the PCIP nucleic acid molecule of claim 1 or the activity of the PCIP polypeptide of claim 8, thereby identifying a compound capable of treating a disorder characterized by
30 aberrant PCIP nucleic acid expression or PCIP protein activity.

24. The method of claim 23, wherein the disorder is a CNS disorder.
25. The method of claim 24, wherein the disorder is epilepsy.
- 5 27. The method of claim 24, wherein the disorder is spinocerebellar ataxia.
28. The method of claim 23, wherein the disorder is a cardiovascular disorder.
- 10 29. The method of claim 28, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.
30. A method for determining if a subject is at risk for a disorder
15 characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity comprising detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion, wherein the genetic lesion is characterized by an alteration affecting the integrity of a gene encoding the PCIP polypeptide of claim 8 or misexpression of the PCIP nucleic acid molecule of claim 1.
- 20 31. The method of claim 30, wherein the disorder is a CNS disorder.
32. The method of claim 31, wherein the disorder is epilepsy.
- 25 33. The method of claim 31, wherein the disorder is spinocerebellar ataxia.
34. The method of claim 30, wherein the disorder is a cardiovascular disorder.
- 30 35. The method of claim 34, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

36. A method for identifying a subject suffering from a disorder characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity comprising obtaining a biological sample from the subject, and detecting in the sample, the presence or absence of a genetic lesion, wherein the genetic lesion is characterized by an alteration affecting the integrity of a gene encoding the PCIP polypeptide of claim 8 or misexpression of the PCIP nucleic acid molecule of claim 1, thereby identifying a subject suffering from a disorder characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity.
37. The method of claim 36, wherein the disorder is a CNS disorder.
38. The method of claim 37, wherein the disorder is epilepsy.
39. The method of claim 37, wherein the disorder is spinocerebellar ataxia.
40. The method of claim 36, wherein the disorder is a cardiovascular disorder.
41. The method of claim 40, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.
42. A method for treating a subject having a potassium channel associated disorder comprising administering to the subject a PCIP polypeptide of claim 8 or portion thereof such that treatment occurs.
43. The method of claim 42, wherein the disorder is a CNS disorder.
44. The method of claim 43, wherein the disorder is epilepsy.
45. The method of claim 43, wherein the disorder is spinocerebellar ataxia.

46. The method of claim 42, wherein the disorder is a cardiovascular disorder.

5 47. The method of claim 46, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

48. A method for treating a subject having a potassium channel associated disorder comprising administering to the subject a nucleic acid encoding a PCIP
10 polypeptide of claim 8 or portion thereof such that treatment occurs.

49. The method of claim 48, wherein the disorder is a CNS disorder.

50. The method of claim 49, wherein the disorder is epilepsy.
15

51. The method of claim 49, wherein the disorder is spinocerebellar ataxia.

52. The method of claim 48, wherein the disorder is a cardiovascular disorder.
20

53. The method of claim 52, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

54. Use of the compound identified in the method of claim 23 to treat a
25 potassium channel associated disorder.

GAATAGCCCCCTTTCAC TTCTGAGTCCC TG CATGTGCGGGCTGAAGAAGAACCCAGAGCCTCCTAGCCTCGCCTCCA
CGTTTGCTGAATACCAAGCTGCAGCGAGCTGCCGGGCGCTTTCTCTCTCCTCAATTACAGATAGACAAACACGGGGAT
TTCTTTCCAGGGTAGGGAGGGCCGGGCCGGGTCCCAACTCGCACTCAAGTCTTCGCTGCCATGGGGCCGTCATGG
GCACCTTCTCATCTCTGCAAAACCAACAAAGGCGACCTCGAAAGATAAGATTGAAGATGAGCTGGAGATGACCATGGTT
TGCCATCGGCCGAGGACTGGAGCAGCTCGAGGCCAGACCAACTTCAACAGAGGAGCTGCAGGTCTCTTATTCGAGG
CTTCAAAAATGAGTGCCCCAGTGGTGTGTCACGAAAGACACATTCAGCAGATCTATGCTCAGTTTTCCTCCATCGAGG
ATGCCAGCACGTATGCCCCATTACCTCTCAATGCCCTTCGACACCACTCAGACGGCTCCGTGAAGTTCGAGGACTTTGTGA
ACCGCTCTGTGATTTATTGAGAGGA ACTGTCCACGAGAACTAAGGTGGACATTTAATTGTATGACATCAACAAGGA
CGGATACATAAA CAAAGAGGAGATGAGACATTGTCAAAGCCATCTATGACATGATGGGAAAATACACATATCCTGTGC
TCAAAGAGGACACTCCAAGGCAGCATGTGGACGTCTCTTCCAGAAAATGGACAAAATAAAGATGGCATCGTAACCTTA
GATGAATTTCTTGAA TCATGT CAGGAGGACGACAAACATCATGAGGTCTCTCCAGTGTTCATAAATGTCACTAATGGT
GACACTCAGCCATT CAGCTCTCAGAGACATTGTACTAAACAACCACTTAACACCCCTGATCTGCCCTTGTCTGATTTTA
CACACCAACTCTTGGACAGAAACACCTTTACACTTTGGAAGAAATTCCTCTGCTGAAGACTTCTTATGGAACCCAGCAT
CATGTGGCTCAGTCTCTGATTGCCAACCTCTTCCCTCTTCTCTCTTTGAGAGACAAAGATGAATTTGAGTTTGTTTTG
GAAGCATGCTCATCTCCTCACACTGCTGCCCTATGGAAGTCCCTCTGCTTAAGCTTAAACAGTAGTGCACAAAATATGC
TGCTTACGTGCCCCAGCCACTGCCCTCCAAGTCAGGCAGACCTTGGTGAATCTGGAAGCAAGAGACCTGAGCCAGATG
CACACCATCTCTGATGGCCCTCCAAACCAATGTGCCCTGTTCTCTTCTTGGTGGGAAAGATGAGAGTTATCCAGAAACA
ATTAGGATCTGT CATGACCAGATTGGGAGAGCCAGCACCTAACATATGTGGGATAGGACTGAATTTAAAGCATGACATT
GTCTGATGACCCAAACTGCCCCG

HUMAN IV PROTEIN

MGAVMGTFFSSLQTKQRRPSKDKIEDLEMTMVCHRPEGLEQAQTNFTKRELQVLYRGFKNECPSGVVNEDTFKQIYAQ
FFPHGDASTYAHYLFNAFDTTQTGSVKFEFVTALSILLRGTVHEKLRWTFNLYDINKDGYINKEEMDIVKAIYDMMGK
YTPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVN

Fig. 1

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RAT 1vN (r1vN) DNA (CD: 339-1037)

GGCACACAACCCCTGGATTCTTCGGAGAATATGCCGTGAGGTGTTGCCAATTATTAGTTCTCTTGGCTAGCAGATGTTTA
GGGACTGGTtaaGCCTTTGGAGAAATTACCTTAGGAAAACGGGGAAATAAAAGCAAAGATTACCATGAATTGCAAGATTA
CCTAGCAATTGCAAGGtagGAGGAGAGAGGTGGAGGGCGGAGTAGACAGGAGGGAGGGAGAAAgtaGAGGAAGCTAGGC
TGGTGGAATAACCCCTGCACTTGGAACAGCGGCAAAGAAGCGCGATTTTCCAGCTTtaaATGCCTGCCCCGCTTCTGCTT
GCCTACCCGGGAACGGAGATGTTGACCCAGGGCGAGTCTGAAGGGCTCCAGACCTTGGGGATAGTAGTGGTCTGTGTTC
CTCTCTGAACTACTGCACTACCTCGGGCTGATTGACTTGTCGGATGACAAGATCGAGGATGATCTGGAGATGACCATGG
TTTGCCATCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACCTTCACCAAGAGAGAACTGCAAGTCCTTTACCGG
GGATTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAGAGACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCATGG
AGATGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTG
TGACTGCTCTGTGATTTTTACTGAGAGGAACGGTCCATGAAAACTGAGGTGGACGTTTAATTTGTACGACATCAATAAA
GACGGCTACATAAAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGGAAATACACCTATCCTGT
GCTCAAAGAGGACACTCCCAGGCAGCACGTGGACGTCTTCTTCCAGAAAATGGATAAAAAATAAAGATGGCATTGTAACGT
TAGACGAATTTCTCGAGTCCTGTCAGGAGGATGACAACATCATGAGGTCTCTACAGCTGTTCCAAAATGTCATGTAAC TG
AGGACACTGGCCATCCTGCTCTCAGAGACACTGACAAACACCTCAATGCCCTGATCTGCCCTTGTTCCAGTTTTACACAT
CAACTCTCGGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCGAGTG
GCTCAGTCTCTGATTGCCAACTCTTCCCTCCCTCCTCCTTGGAGAGGGACGAGCTGAAATCCGAAGTTTGTTTTGGAAGC
ATGCCCATCTCTCCATGCTGCTGCTGCCCTGTGGAAGGCCCTCTGCTTGAGCTTAAACAGTAGTGCACAGTTTTCTGCG
TATACAGATCCCCAACTCACTGCCTCTAAGTCAGGCAGACCCTGATCAATCTGAACCAAATGTGCACCATCCTCCGATGG
CCTCCCAAGCCAATGTGCCTGCTTCTCTTCCCTCTGGTGGGAAGAAAGAACGCTCTACAGAGCACTTAGAGCTTACCATGA
AAATACTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGGTATCAGATGATGCAACA
GCCCATGTCAATTTTTTTTTTCCAGAGGTAGGGACTAATAATTCTCCACACTAGCACCTACGATCATAGAACAAGTCTTTT
AACACATCCAGGAGGGAAACCGCTGCCCAGTGGTCTATCCCTTCTCTCCATCCCTGCTCAAGCCCAGCACTGCATGTCT
CTCCCGGAAGGTCCAGAATGCCTGTGAAATGCTGTAACTTTTATACCCTGTTATAATCAATAAACAGAACTATTTCTGTAC
AAAAAAAAAAAAAAAA

Fig. 2

SUBSTITUTE SHEET (RULE 26)

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RAT 1vN (r1vN) PROTEIN

MLTQGESEGLQTLGIVVVLCSKLLHYLGLIDLSDDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC
PSGVVNEETFKQIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINK
EEMMDIVKAIYDMMGKYTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVN

Fig. 2 Continued

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MOUSE 1V (CD:477-1127)

CGGCCCCCTGAGATCCAGCCCCGAGCGCGGGGCGGAGCGGCCGGGTGGCAGCAGGGGCGGGCGGGCGGAGCGCAGCTCCCC
CACCGCACGCGGCGCGGGCTCGGCAGCCTCGGCCGTGCGGGCACGCCGGCCCCGTGTCCAACATCAGGCAGGCTTTGGGG
CTCGGGGCTCGGGCCTCGGAGAAGCCAGTGGCCCCGGCTGGGTGCCCCGACCGGGGGGCGCCTGTCAAGGCTCCCCGCGAGC
CTCTGGCCCTGGGAGTCAGTGCATGTGCCTGGCTGAAGAAGGCAGCAGCCACGAGCTCCAGGCGCCCCGGCCCCACGTTT
TCTGAATACCAAGCTGCAGGCGAGCTGCTCGGGGCTTTTTTGCTTTCTCGCTTTTCTCTCCTCCAATTCAAAGTGGGCA
ATCCACACCGATTTCTTTTCAGGGGAGGGAAGAGACAGGGCCTGGGGTCCCAAGACGCACACAAGTCTTCGCTGCCATGG
GGGCCGTATGGGCACTTTCTCCTCCCTGCAGACCAAACAAAGGCGACCCTCTAAAGACAAGATTGAGGATGAGCTAGAG
ATGACCATGGTTTGGCACCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAACTGCAAGT
CTTGTACCGGGGATTCAAAAACGAGTGCCCTAGCGGTGTGGTCAATGAAGAAACATTCAAGCAGATCTACGCTCAGTTTT
TCCCTCACGGAGATGCCAGCACATATGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTC
GAGGACTTTGTGACTGCTCTGTGATTTTACTGAGAGGGACAGTCCATGAAAACTAAGGTGGACGTTTAATTTGTATGA
CATCAATAAAGACGGCTACATAAACAAAGAGGAGATGATGGACATAGTCAAAGCCATCTATGACATGATGGGGAAATACA
CCTATCCTGTGCTCAAAGAGGACACTCCCAGGCAGCATGTGGATGTCTTCTTCCAGAAAATGGATAAAAAATAAGATGGC
ATTGTAACGTTAGATGAATTTCTTGAATCATGTCAGGAGGATGACAACATCATGAGATCTCTACAGCTGTTCCAAAATGT
CATGTAACTGAGGACACTGGCCATTCTGCTCTCAGAGACACTGACAAACACCTTAATGCCCTGATCTGCCCTTGTTCCAA
TTTTACACACCAACTCTTGGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTG
GCACCACGTGGCTCTGTCTCTGAGGGACGAGCGGAGATCCGACTTTGTTTTGGAAGCATGCCCATCTCTTCATGCTGCTG
CCCTGTGGAAGGCCCCCTCTGCTTGAGCTTAATCAATAGTGACAGTTTTATGCTTACACATATCCCCAACTCACTGCCCTC
CAAGTCAGGCAGACTCTGATGAATCTGAGCCAAATGTGCACCATCCTCCGATGGCCTCCCAAGCCAATGTGCCTGCTTCT
CTTCTCTGGTGGGAAGAAAGAGTGTCTACGGAACAATTAGAGCTTACCATGAAAATATTGGGAGAGGCAGCACCTAAC
ACATGTAGAATAGGACTGAATTATTAAGCATGGTGATATCAGATGATGCAAATTGCCCATGTCAATTTTTTTCAAAGGTAG
GGACAAATGATTCTCCACACTAGCACCTGTGGTCATAGAGCAAGTCTCTTAACATGCCCAGAAGGGGAACCACTGTCCA
GTGGTCTATCCCTCCTCTCCATCCCCTGCTCAAACCCAGCACTGCATGTCCCTCCAAGAAGGTCCAGAATGCCTGCGAAA
CGCTGTACTTTTATACCCTGTTCTAATCAATAAACAGAACTATTTTCGTAAAAAAAAAAAAAAAAAAAAA

MOUSE 1V PROTEIN

MGAVMGTFSSLQTKQRRPSKDKIEDELEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVVNEETFQKIY AQ
FFPHGDASTYAHYLFNAFDTTQTGSKVFEDFVTALSILLRGTVEKLRWTFNLYDINKDGYINKEEMMDIVKAIYDMMGK
VTYPVLKEDTPRQHVVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNV

Fig. 3

SUBSTITUTE SHEET (RULE 26)

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RAT 1VL DNA (CD:31-714)

GTCCCAAGTCGCACACAAGTCTTCGCTGCCATGGGGGCCGTCATGGGTACCTTCTCGTCCCTGCAGACCAAACAAAGGCG
ACCTCTAAAGACATCGCCTGGTGGTATTACCAGTATCAGAGAGACAAGATCGAGGATGATCTGGAGATGACCATGGTTT
GCCATCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAACTGCAAGTCCTTTACCGGGGA
TTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAGAGACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCATGGAGA
TGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCAACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTGTGA
CTGCTCTGTGATTTTACTGAGAGGAACGGTCCATGAAAACTGAGGTGGACGTTTAATTTGTACGACATCAATAAAGAC
GGCTACATAAAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGGAAATACACCTATCCTGTGCT
CAAAGAGGACACTCCCAGGCAGCACGTGGACGTCTTCTTCCAGAAAATGGATAAAAATAAAGATGGCATTGTAACGTTAG
ACGAATTTCTCGAGTCCTGTCAGGAGGATGACAACATCATGAGGTCTCTACAGCTGTTCCAAAATGTCATGTAAGTGGG
ACACTGGCCATCCTGCTCTCAGAGACACTGACAAACACCTCAATGCCCTGATCTGCCCTTGTTCCAGTTTTACACATCAA
CTCTCGGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTCTACAAAACCTGGCACCGCGTGGCT
CAGTCTCTGATTGCCAACTCTTCCTCCCTCCTCCTCTTGAGAGGGACGAGCTGAAATCCGAAGTTTGTTTTGAAGCATG
CCCATCTCTCCATGCTGCTGCTGCCCTGTGGAAGGCCCTCTGCTTGAGCTTAAACAGTAGTGACAGTTTTCTGCGTAT
ACAGATCCCCAACTCACTGCCTCTAAGTCAGGCAGACCCTGATCAATCTGAACCAAATGTGCACCATCCTCCGATGGCCT
CCCAAGCCAATGTGCCTGCTTCTCTTCTCTGGTGGGAAGAAAGAACGCTCTACAGAGCACTTAGAGCTTACCATGAAAA
TACTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGGTATCAGATGATGCAAACAGCC
CATGTCAATTTTTTTTCCAGAGGTAGGGACTAATAATTCTCCACACTAGCACCTACGATCATAGAACAAGTCTTTTAAACA
CATCCAGGAGGGAAACCGCTGCCAGTGGTCTATCCCTTCTCTCCATCCCCTGCTCAAGCCCAGCACTGCATGTCTCTCC
CGGAAGGTCCAGAATGCCTGTGAAATGCTGTAACTTTTATACCCTGTTATAATCAATAAACAGAACTATTTTCGTACAAAA
AAAAAAAAAAAAAA

RAT 1VL PROTEIN

MGAVMGTFSSLQTKQRRPSKDIWWYYQYQRDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVV
NEETFQKIYAQFFPHGDASTYAHYLFNAFDTTQTGSKVFEDFVTALSILLRGTVEKLRWTFNLYDINKDGYINKEEMMD
IVKAIYDMMGKYTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVN

Fig. 4

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MOUSE 1VL DNA (CD:77-760)

ATCCACACCGATTTCTTTTCAGGGGAGGGAAGAGACAGGGCCTGGGGTCCCAAGACGCACACAAGTCTTCGCTGCCATGG
GGGCCGTCATGGGCACTTTCTCCTCCCTGCAGACCAAACAAAGGCGACCTCTAAAGACATCGCCTGGTGGTATTACCAG
TATCAGAGAGACAAGATTGAGGATGAGCTAGAGATGACCATGGTTTGCCACCGGCCTGAGGGACTGGAGCAGCTTGAGGC
ACAGACGAACTTCACCAAGAGAGAACTGCAAGTCTTGTACCGGGGATTCAAAAACGAGTGCCCTAGCGGTGTGGTCAATG
AAGAAACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCACGGAGATGCCAGCACATATGCACATTACCTCTTCAATGCC
TTCGACACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTGTGACTGCTCTGTCTGATTTTACTGAGAGGGACAGTCCA
TGAAAACTAAGGTGGACGTTTAATTTGTATGACATCAATAAAGACGGCTACATAAACAAGAGGAGATGATGGACATAG
TCAAAGCCATCTATGACATGATGGGGAAAATACACCTATCCTGTGCTCAAAGAGGACACTCCCAGGCAGCATGTGGATGTC
TTCTTCCAGAAAATGGATAAAAATAAAGATGGCATTGTAACGTTAGATGAATTTCTTGAATCATGTCAGGAGGATGACAA
CATCATGAGATCTCTACAGCTGTTCCAAAATGTCATGTAAGTGAAGGACACTGGCCATTCTGCTCTCAGAGACACTGACAA
ACACCTTAATGCCCTGATCTGCCCTTGTTCCAATTTTACACACCAACTCTTGGGACAGAAATACCTTTTACACTTTGGAA
GAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCACGTGGCTCTGTCTCTGAGGGACGAGCGGAGATCCGACTTTG
TTTTGGAAGCATGCCCATCTCTTCATGCTGCTGCCCTGTGGAAGGCCCTCTGCTTGAGCTTAATCAATAGTGCACAGTT
TTATGCTTACACATATCCCCAACTCACTGCCTCCAAGTCAGGCAGACTCTGATGAATCTGAGCCAAATGTGCACCATCCT
CCGATGGCCTCCCAAGCCAATGTGCCTGCTTCTCTTCCCTCTGGTGGGAAGAAAGAGTGTCTACGGAACAATTAGAGCTT
ACCATGAAAATATTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGATATCAGATGAT
GCAAATTGCCCATGTCATTTTTTTCAAAGGTAGGGACAAATGATTCTCCACACTAGCACCTGTGGTCATAGAGCAAGTC
TCTTAACATGCCCAGAAGGGGAACCACTGTCCAGTGGTCTATCCCTCCTCTCCATCCCCTGCTCAAACCCAGCACTGCAT
GTCCCTCCAAGAAGGTCCAGAAATGCCTGCGAAACGCTGTACTTTTATACCCTGTTCTAATCAATAAACAGAACTATTTG
TACAAAAAAAAAAAAAAAAAAAA

MOUSE 1VL PROTEIN

MGAVMGTFSSLQTKQRRPSKDIAWYYYQYQRDKIEDELEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVV
NEETFKQIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINKEEMMD
IVKAIYDMMGKYTYPVLKEDTPRQHVDFVQKMDKNKDGIIVTLDEFLESCQEDDNIMRSLQLFQNVN

Fig. 5

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RAT 1VN DNA (FIRST-PASS, PARTIAL; CD: 345-955)

GTCCGGGCACACAACCCCTGGATTCTTCGGAGAATATGCCGTGACGGTGTTGCCAATTATTAGTTCTCTTGGCTAGCAGA
TGTTTAGGGACTGGTTAAGCCTTTGGAGAAATTACCTTAGGAAAACGGGGAAATAAAAAGCAAAGATTACCATGAATTGCA
AGATTACCTAGCAATTGCAAGGTAGGAGGAGAGAGGTGGAGGGCGGAGTAGACAGGAGGGAGGGAGAAAGTGAGAGGAAG
CTAGGCTGGTGGAAATAACCCCTGCACTTGGAACAGCGGCAAAGAAGCGCGATTTTCCAGCTTTAAATGCCTGCCCCGCGTT
CTGCTTGCCTACCCGGGAACGGAGATGTTGACCCAGGGCGAGTCTGAAGGGCTCCAGACCTTGGGGATAGTAGTGGTCCT
GTGTTCCCTCTCTGAAACTACTGCACTACCTCGGGCTGATTGACTTGTTCGGATGACAAGATCGAGGATGATCTGGAGATGA
CCATGGTTTGCCATCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAACTGCAAGTCCTT
TACCGGGGATTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAGAGACATTCAAGCNGATCTACGCTCAGTTTTTCCC
TCATGGAGATGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTTCGAGG
ACTTTGTGACTGCTCTGTTCGATTTTACTGAGAGGAACGGTCCATGAAAACTGAAGTGGACGTTTAATTTGTACGACATC
AATAAAGACGGCTACATAAACAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGGAAATACACCTA
TCTTGTGCTCAAAGAGGACACTTCCAGGCAGCACGTGGACGTCTTCTTCCAGAAAATGGATAAAAATAAAGATGG

RAT 1VN PROTEIN (PARTIAL)

MLTQGESEGLQTLGIVVVLCSLKLHLYLGLIDLSDDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC
PSGVVNEETFKXIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKWKWTFNLYDINKDGYINK
EEMMDIVKAIYDMMGKYTYLVLKEDTSRQHVVDVFFQKMDKNKD

Fig. 6

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HUMAN 9QL DNA (CD:207-1019)
CTCACCTGCTGCCTAGTGTTCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCCGGGCCCATTCCCAGACTCA
GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACC
CGGCGCCCCCTCCCACGGCCCCGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTTTGTCCG
ATTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGGCCACCCTCCAGGGCCCCTAAAAAGCGCTGAAGCAGCGA
TTCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCCGCCCCAGCCTCCCTCCG
CCCCACAGACCCCGCCTGCTGGACCCAGACAGCGTGGACGATGAATTTGAATTGTCCACCGTGTGTACCGGCCTGAGG
GTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCTGTACCGGGGCTTCAAGAACGAATGT
CCCAGCGGAATTGTCAATGAGGAGAACTTCAAGCAGATTTACTCCCAGTTCTTTCTCAAGGAGACTCCAGCACCTATGC
CACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGAGGACTTTGTGGCTGGTTTGTCCGTGA
TTCTTCGGGGAAGTGTAGATGACAGGCTTAATTGGGCCCTTCAACCTGTATGACCTTAACAAGGACGGCTGCATCACCAAG
GAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACGTACCTTGCCTCCGGGAGGAGGCCCC
AAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAAACAAGGATGGTGTGGTGACCATTGAGGAATTCATTGAGT
CTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCTATCTAGCCCCCAGGAGAGGGGGTCAGT
GTTTCTTGGGGGACCATGCTCTAACCCTAGTCCAGGCGGACCTCACCTTCTCTTCCCAGGTCTATCCTCATCCTACGC
CTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTGAGTAGTCCAGATCTCTGGAGCTGAAGGGGCCAGAGAGTGGG
CAGAGTGCATCTCGGGGGGTGTTCCCAACTCCACCAGCTCTCACCCCTTCTGCTGACACCCAGTGTTGAGAGTGCC
CCTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTACCTACTCTAGAAACACACTAGAGCGATGTCTCCTGCTATGGTGC
TTCCCCCATCCCTGACCTCATAAACATTTCCCCTAAGACTCCCCTCTCAGAGAGAATGCTCCATTCTTGGCACTGGCTGG
CTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCCTGAGTCAATGGA
TAGGTCCTAGGAGGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCAGGTTATAGCT
CCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAGAAGACCTTGTCTCCTTAGAAA
TGCCCCAGAAATTTTCCACACCCCTCCTCGGTATCCATGGAGAGCCTGGGGCCAGATATCTGGCTCATCTCTGGCATTGCT
TCCTCTCCTTCTCCTGCTGCTGTTGGTGGTGGTGTGGTGGGGGAATGTGGATGGGGGATGTCTGGCTGATGCCTGC
CAAAATTCATCCCACCCCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACTTGAGTTTTTGTTCCTCATGTTCTCTA
TAGACTTGGGACCTTCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAAGGAGGGAGGC
AGGCATAGC

Fig. 7

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HUMAN 9QL PROTEIN

MRGQGRKESLSDSRDL DGSYDQLTGHPGPTKKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPRLLD PDSVDDE
FELSTVCHRPEGLEQLQEQT KFKELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSTYATFLFNAFD TNHDGSV
SFEDFVAGLSVILRGTVDDRLNWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDR NK
DGVVTIEEFIESCQKDENIMRSMQLFDNVI

Fig. 7 Continued

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RAT 9QL DNA (PARTIAL;CD:2-775)

CCGAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCCCTCCAGGGCCCAGTAAAAAGCCCTGAAGCAGCGTTTCC
TCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCTGCCCCAGCCTCCCTCCGCCCC
CACAGACCCCGCCCGCTGGACCCAGACAGCGTAGAGGATGAGTTTGAATTATCCACGGTGTGTCACCGACCTGAGGGCCT
GGAACAACCTCCAGGAACAGACCAAGTTCACACGCAGAGAGCTGCAGGTCTGTACCGAGGCTTCAAGAACGAATGCCCCA
GTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACT
TTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTCAAGTTTGTAGGACTTTGTGGCTGGTTTGTGCGGTGATTCT
TCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTATATGACCTCAACAAGGACGGCTGTATCACAAAGGAGG
AAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAAGTACACATACCCTGCCCTCCGGGAGGAGGCCCAAGA
GAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAGGACGGCGTGGTGACCATCGAGGAATTCATCGAGTCTTG
TCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTTTGATAATGTCATCTAGCTCCCCAGGGAGAGGGGTTAGTGTG
TCCTAGGGTGACCAGGCTGTAGTCCTAGTCCAGACGAACCTAACCCCTCTCTCTCCAGGCCTGTCCATCTTACCTGTAC
CCTGGGGGCTGTAGGGATTCAATATCCTGGGGCTTCAGTAGTCCAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGT
AGGCAAGCTAAATCTGGGGGCTTCCCAACCCCGACAGCTCTCACCCCTTCTCAACTGATACCTAGTGCTGAGGACACCC
CTGGTGTAGGGACCAAGTGGTTCTCCACCTTCTAGTCCCACTCTAGAAACCACATTAGACAGAAGGTCTCCTGCTATGGT
GCTTTCCCATCCCTAATCTCTTAGATTTTCTCAAGACTCCCTTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGG
GGACATGGACAGAGCGTGTTCTCTAGTTCTAGATCGCGAGCGGCCGC

RAT 9QL PROTEIN (PARTIAL)

RDLDGSYDQLTGHPPGPSKKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPRPLDPDSVEDEFELSTVCHRPEGL
EQLQEQTkFTRRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSVSFEDFVAGLSVIL
RGTIDDRLSWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTPALREEAPREHVESFFQKMDRNKDGVTIEEFIESC
QQDENIMRSMQLFDNVI

Fig. 8

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MOUSE 9QL DNA (CD:181-993)

CGGGACTCTGAGGTGGGCCCCATAAATCCAGCGCTCCCCAGAGAAAAGCCTTGCCAGCCCCTACTCCCGGCCCCCAGCCCC
AGCAGGTCGCTGCGCCGCCAGGGGGCACTGTGTGAGCGCCCTATCCTGGCCACCCGGCGCCCCCTCCCACGGCCCAGGCG
GGAGCGGGGCGCCGGGGGCCATGCGGGGCCAAGGCCGAAAGGAGAGTTTGTCCGAATCCCGAGATTTGGACGGCTCCTAT
GACCAGCTTACGGGCCACCCTCCAGGGCCCAGTAAAAAGCCCTGAAGCAGCGTTTCCTCAAGCTGCTGCCGTGCTGCGG
GCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCTGCCCCAGCCTCCCTCCGCCCCACAGACCCGCCCCGCTGGACC
CAGACAGCGTGGAGGATGAGTTTGAACATATCCACGGTGTGCCACCGGCCTGAGGGTCTGGAACAACTCCAGGAACAAACC
AAGTTCACACGCAGAGAGTTGCAGGTCCTGTACAGAGGCTTCAAGAACGAATGTCCCAGCGGAATTGTCAACGAGGAGAA
CTTCAAGCAAATTTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTACGCTACTTTTCTCTTCAATGCCTTTGACA
CCAACCATGATGGCTCTGTGCTAGTTTGTGAGGACTTTGTGGCTGGTTTGTGCTGATTCTTCGGGGGAACCATAGATGATAGA
CTGAACTGGGCTTTCAACTTATATGACCTCAACAAGGATGGCTGTATCAGGAAGGAGGAAATGCTCGACATCATGAAGTC
CATCTATGACATGATGGGCAAGTACACCTACCCTGCCCTCCGGGAGGAGGCCCCGAGGGAACACGTGGAGAGCTTCTTCC
AGAAGATGGACAGAAACAAGGACGGCGTGGTGACCATTTAGGAATTCATTGAGTCTTGTCAACAGGACGAGAACATCATG
AGGTCCATGCAACTCTTTGATAATGTCATCTAGCTCCCCAGGGAGAGGGGTTAGTGTGTCCCAGGGTAACCATGCTGTAG
CCCTAGTCCAGGCAAACCTAACCTCCTCTCCCCGGGTCTGTCTCATCCTACCTGTACCTGAGGGGCTGTAGGGATTCA
ACATCCTGGCGCTTCAGTAGTCCAGATCCCTGAGCTAAGTGGCGAGAGTAGGCAAGCTAAGTCTTTGGAGGGTGGGTGGG
GGCGCGCAGATTCCCAACCCCCGACGACTCTCACCCCTTTCTCGACTGATACCCAGTGCTGAGGCTACCCCTGGTGTGCG
GAACGACCAAAGTGGTTCTCTGCCTCCCCAGCCCACTCTAGAGACCCACACTAGACGGGAATATCTCCTGCTATGGTGCT
TTCCCCATCCCTGACCGCAGATTTTCTCCTAAGACTCCCTTCTCAGAGAATATGCTTTTGTCCCTTGTCCCTGGCTGGC
TTTTCAGCCTAGCCTTTGAGGACCCTGTGGGAGGGGAGAATAAGAAAGCAGACAAAATCTTGGCCCTGAGCCAGTGGTTA
GGTCTTAGGAATCAGGCTGGAGTGGAGACCAGAAAGCCTGGGCAGGCTATGAGAGCCCCAGGTTGGCTTGTACCGCCAG
GTTCCACAGGGCTGCTGCTCTGGGTCAGCAGAGTATGAGTTTCCAGACTTTCCAGAAGGCCTTATGTCCCTTAGCAATGTC
CCAGAAATTCACCATACTTCTCAGTGTCTTAGGATCCAGATGTCCGGTCCATCCCTGAAACCTCTCCCTCCTCCTTGC
TCCTATGGTGGGAGTGGTGGCCAGGGGACGATGAGTGAGCCGGTGTCTGGATGATGCCTGTCAAGGTCCCACCTACCCT
CCGGCTGTCAAGCCGTTCTGGTGACCCTGTTTGAATTCTCCATGACCCCTGTCTAGATGTAGAGGTGTGGAGTGAGTCTAG
TGGCAGCCTTAGGGGAATGGGAAGAACGAGAGGGGCACTCCATCTGAACCCAGTGTGGGGGCATCCATTGCAATCTTTGC
CTGGCTCCCCACAATGCCCTAGGATCCTCTAGGGTCCCCACCCCACTCTTTAGTCTACCCAGAGATGCTCCAGAGCTCA
CCTAGAGGGCAGGGACCATAGGATCCAGGTCCAACCTGTCTATCAGCATCCGGCCATGCTGCTGCTGCTTATTAATAAACC
TGCTTGTGCTTCAGCGCCCCCTTCCCAGTCAGCCAGGGTCTGAGGGGAAGGCCCCCACTTTCCCGCCTCCTGTCAGACATT
GTTGACTGCTTTGCATTTTGGGCTCTTCTACCTATATTTTGTATAATAAGAAAGACACCAGATCCAATAAAACACATGGC
TATGCACAAAAAAAAAAAAAAAAA

MOUSE 9QL PROTEIN

MRGQGRKESLSERDLDSYDQLTGHPGPSKKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPRPLDPDSVEDE
FELSTVCHRPEGLEQLQEQTFRRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDSV
SFEDFVAGLSVILRGTTIDRLNWFNLYDLNKDGCITKEMLDIMKSIYDMMGKYTPALREEAPREHVESFFQKMDRDK
DGVVTIEEFIESCQQDENIMRSMQLFDNVI

Fig. 9

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HUMAN 9QM DNA (CD:207-965)

CTCACCTGCTGCCTAGTGTTCCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTTCCAGACTCA
GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACC
CGGCGCCCCCTCCCACGGCCCCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTTTGTCCG
ATTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGGCCACCCTCCAGGGCCCACTAAAAAGCGCTGAAGCAGCGA
TTCCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAACAGCGTGGACGATGAATTTGAATT
GTCCACCGTGTGTCACCGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCC
TGTACCGGGGCTTCAAGAACGAATGTCCCAGCGGAATTGTCAATGAGGAGAACTTCAAGCAGATTTACTCCCAGTTCTTT
CCTCAAGGAGACTCCAGCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGA
GGACTTTGTGGCTGGTTTGTCCGTGATTCTTCGGGGAAGTGTAGATGACAGGCTTAATTGGGCCTTCAACCTGTATGACC
TTAACAAGGACGGCTGCATCACCAAGGAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACG
TACCCTGCACTCCGGGAGGAGGCCCCAAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAAACAAGGATGGTGT
GGTGACCATTGAGGAATTCATTGAGTCTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCA
TCTAGCCCCCAGGAGAGGGGGTCAGTGTTTCTCGGGGGGACCATGCTCTAACCTAGTCCAGGGCGACCTCACCTTCTC
TTCCAGGTCTATCCTCATCCTACGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCACTAGTCCAGATCTC
TGGAGCTGAAGGGGCCAGAGAGTGGGCAGAGTGCATCTCGGGGGGTGTTCCCAACTCCCACCAGCTCTCACCCCTTCTC
GCCTGACACCCAGTGTTGAGAGTGGCCCTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTACCCTACTCTAGAAACACAC
TAGAGCGATGTCTCCTGCTATGGTGCTTCCCCATCCCTGACCTCATAAACATTTCCCCTAAGACTCCCCTCTCAGAGAG
AATGCTCCATTCTTGGCACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGG
AGAAATCTTGGGCCTGAGTCAATGGATAGGTCCTAGGAGGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGA
TTGCTCAGGCATACCAGGTTATAGCTCCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTT
TGCAGAAGACCTTGTCTCCTTAGAAATGCCCCAGAAATTTTCCACACCTCCTCGGTATCCATGGAGAGCCTGGGGCCAG
ATATCTGGCTCATCTCTGGCATTGCTTCCTCTCCTTCCCTTCCCTGCATGTGTTGGTGGTGGTGTGGTGGGGGAATGTGGA
TGGGGGATGTCTGGCTGATGCCTGCCAAAATTTTCATCCCACCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACT
TGAGTTTTTGTTCCTCATGTTCTCTATAGACTTGGGACCTTCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCT
TAGAAGGGAGAGGGAAGGAGGGAGGCAGGCATAGC

Fig. 10

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HUMAN 9QM PROTEIN

MRGQGRKESLSDSRDL DGSYDQLTGHPPGPTKKALKQRFLKLLPCCGPQALPSVSENSVDDEFELSTVCHRPEGLEQLQE
QTKFTRKELQVLYRGFKNECP SGIVNEENFKQIYSQFFPQGDSSTYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTV D
DRLNWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNKDG VVTIEEFIESCQK DEN
IMRSMQLFDNVI

Fig. 10 Continued

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RAT 9QM DNA (CD:214-972)

CTCACTTGCTGCCCAAGGCTCCTGCTCCTGCCCCAGGACTCTGAGGTGGGCCCTAAAACCCAGCGCTCTCTAAAGAAAAG
CCTTGCCAGCCCCCTACTCCCGGCCCCCAACCCAGCAGGTGCTGCGCCGCCAGGGGGCGCTGTGTGAGCGCCCTATTCT
GGCCACCCGGCGCCCCCTCCACGGCCCAGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAAGGCAGAAAGGAGAGT
TTGTCCGAATCCCGAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCCCTCAGGGGCCAGTAAAAAGCCCTGAA
GCAGCGTTTCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAACAGCGTAGAGGATGAGT
TTGAATTATCCACGGTGTGTACCGACCTGAGGGCCTGGAACAACCTCAGGAACAGACCAAGTTCACACGCAGAGAGCTG
CAGGTCTGTACCGAGGCTTCAAGAACGAATGCCCCAGTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTTATTCTCA
GTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTCA
GTTTTGAGGACTTTGTGGCTGGTTTGTGCGGTGATTCTTCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTA
TATGACCTCAACAAGGACGGCTGTATCACAAAGGAGGAAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAA
GTACACATACCCTGCCCTCCGGGAGGAGGCCCCAAGAGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAGG
ACGGCGTGTTGACCATCGAGGAATTCATCGAGTCTTGTCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTTTGAT
AATGTCATCTAGCTCCCCAGGGAGAGGGGTAGTGTGCTTAGGGTGACCAGGCTGTAGTCCTAGTCCAGACGAACCTAA
CCCTCTCTCTCAGGCTGTCTCATCTTACCTGTACCCTGGGGGCTGTAGGGATTCAATATCCTGGGGCTTCAGTAGTC
CAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGTAGGCAAGCTAAATCTGGGGGCTTCCCCAACCCCGACAGCTCTC
ACCCCTTCTCAACTGATACCTAGTGCTGAGGACACCCCTGGTGTAGGGACCAAGTGGTTCTCCACCTTCTAGTCCCACTC
TAGAAACCACATTAGACAGAAGGTCTCCTGCTATGGTGCTTTCCCCATCCCTAATCTCTTAGATTTTCTCAAGACTCCC
TTCTCAGAGAACACGCTCTGTCCATGTCCCAGCTGGCTTCTCAGCCTAGCCTTTGAGGGCCCTGTGGGGAGGCGGGGAC
AAGAAAGCAGAAAAGTCTTGGCCCCGAGCCAGTGGTTAGGTCTAGGAATTGGCTGGAGTGGAGGCCAGAAAGCCTGGGC
AGATGATGAGAGCCCAGCTGGGCTGTCACTGCAGGTTCGGGGGCTACAGCCCTGGGTGAGCAGAGTATGAGTTCCAGA
CTTTCCAGAAGGTCTTAGCAATGTCCCAGAAATTCACCGTACACTTCTCAGTGTCTTAGGAGGGCCCGGGATCCAGATG
TCTGGTTTCATCCCTGAATCCTCTCCCTCCTTCTTGCTCGTATGGTGGGAGTGGTGGCCAGGGGAAGATGAGTGGTGTCCC
GGATGATGCCTGTCAAGGTCCCACCTCCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCTCCATGACCCCTATCTAGA
TG TAGAGGCATGGAGTGAAGTACAGGATTTCCCGAAGTTGAGTTTTTACCCTCCTCCTAGTGGCTGCCCTAGGGGAATGGG
AAGAACCAGTGTGGGGGCACCCATTAGAATCTTTGCCCGGCTCCTCACAATGCCCTAGGGTCCCCTAGGGTACCCGCTC
CCTCTGTTTAGTCTACCCAGAGATGCTCCTGAGCTCACCTAGAGGGTAGGGACGGTAGGCTCCAGGTCCAACCTCTCCAG
GTCAGCACCTGCCATGCTGCTGCTCCTCATTAACAAACCTGCTTGTCTCCTCCTGCGCCCCCTTCTCAGTCAGCCAGGGT
CTGAGGGGAAGGGCTCCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTTGCATTTTGGGCTCTTCTATCTATTTTG
TAAATAAGACATCAGATCCAATAAAACACACGGCTATGCACAAAAAAAAAAAAAAAAAAAA

RAT 9QM PROTEIN

MRGQGRKESLSESRDLGSDYDQLTGHPGPSKKALKQRFLKLLPCCGPQALPSVSENSVEDEFELSTVCHRPEGLEQLQE
QTKFTRRELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSSNYATFLNAFDTNHDGSVSFEDFVAGLSVILRGITD
DRLSWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNDKGVVTTIEEFIESCQQDEN
IMRSMQLFDNVI

Fig. 11

SUBSTITUTE SHEET (RULE 26)

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HUMAN 9QS DNA (CD:207-869)

CTCACCTGCTGCCTAGTGTTCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTTCCAGACTCA
GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACC
CGGCGCCCCCTCCACGGCCCCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTTTGTCCG
ATTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGACAGCGTGGACGATGAATTTGAATTGTCCACCGTGTGTCAC
CGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCCTGTACCGGGGCTTCAA
GAACGAATGTCCCAGCGGAATTGTCAATGAGGAGAACTTCAAGCAGATTTACTCCCAGTTCTTTCCTCAAGGAGACTCCA
GCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTGAGTTTTGAGGACTTTGTGGCTGGT
TTGTCCGTGATTCTTCGGGGAAGTGTAGATGACAGGCTTAATTGGGCCTTCAACCTGTATGACCTTAACAAGGACGGCTG
CATCACCAGGAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACGTACCCTGCACTCCGGG
AGGAGGCCCAAGGGAACACGTGGAGAGCTTCTTCAGAAGATGGACAGAAACAAGGATGGTGTGGTGACCATTGAGGAA
TTCATTGAGTCTTGTCAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCATCTAGCCCCCAGGAGA
GGGGGTCAGTGTTCCTGGGGGGACCATGCTCTAACCCTAGTCCAGGCGGACCTCACCCCTTCTCTTCCCAGGTCTATCCT
CATCCTACGCCTCCCTGGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTGAGTAGTCCAGATCTCTGGAGCTGAAGGGGCC
AGAGAGTGGGCAGAGTGCATCTCGGGGGGTGTTCCCAACTCCCACCAGCTCTCACCCCTTCTCTTCCCAGGTCTATCCT
TGAGAGTGCCCCCTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTACCCCTACTCTAGAAACACACTAGAGCGATGTCTCCT
GCTATGGTGCTTCCCCCATCCCTGACCTCATAAACATTTCCCCTAAGACTCCCCTCTCAGAGAGAATGCTCCATTCTTGG
CACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCCTG
AGTCAATGGATAGGTCCTAGGAGGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCA
GGTTATAGCTCCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAGAAGACCTTGTC
TCCTTAGAAATGCCCCAGAAATTTCCACACCCTCCTCGGTATCCATGGAGAGCCTGGGGCCAGATATCTGGCTCATCTC
TGGCATTGCTTCCTCTCCTTCCTTCCTGCATGTGTTGGTGGTGGTTGTGGTGGGGGAATGTGGATGGGGGATGTCTGGC
TGATGCCTGCCAAAATTTTCATCCCACCCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACTTGAGTTTTTGTTCCTC
ATGTTCTCTATAGACTTGGGACCTTCCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAA
GGAGGGAGGCAGGCATAGC

Fig. 12

SUBSTITUTE SHEET (RULE 26)

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MONKEY 9QS DNA (CD:133-795)

CCCACGCGTCCGCCCACGCGTCCGCGGACGCGTGCGGTGCACTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCG
GCCACCCGGCGCCCCCTCCACGGACCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTT
TGTCGGATTCCCGAGACCTGGACGGATCCTACGACCAGCTCACGGACAGCGTGGAGGATGAATTTGAATTGTCCACCGTG
TGTCACCGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCCTGTACCGGGG
CTTCAAGAACGAATGTCCGAGCGGAATTGTCAATGAGGAGAACTTCAAGCAAATTTACTCCCAGTTCTTTCTCAAGGAG
ACTCCAGCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGAGGACTTTGTG
GCTGGTTTGTCCGTGATTCTTCGGGGAACTGTAGATGACAGGCTTAATTGGGCCTTCAACTTGTATGACCTCAACAAGGA
CGGCTGCATCACCAAGGAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACATACCCTGCAC
TCCGGGAGGAGGCCCAAGGGAACATGTGGAGAATTCTTCCAGAAGATGGACAGAAACAAGGATGGCGTGGTGACCATT
GAGGAATTCATTGAGTCTTGTCAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCATCTAGCCCCC
AGGAGAGGGGGTCAGTGTTTCTGGGGGACCATGCTCTAACCTAGTCCAGGTGGACCTCACCTTCTCTTCCCAGGTC
TATCCTTGTCCTAGGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCACTAGTCCAGATCTCTGGAGCTGAA
GGGGCCAGAGAGTGGGCAGAGTGCATCTTGGGGGTGTTCCCACTCCCACCAGCTTTCACCCGCTTCTGCCTGACACC
CAGTGTTGAGAGTGCCCCCTCCTGTAGGAACGTAGTGGTTCCTTCCACCTCCTTACCCCACTCTAGAAACACACTAGACAGAT
GTCTCGTGCTATGGTGCTTCCCCCATCCCTGACTTCATAAACATTTCCCTTAAACTCCCTTCTCAGAGAGAATGCTCCA
TTCTTGGCACTGGCTGGCTTCTCAGACCAGCCTTTGAGAGCCCTGTGGGAGGGGACAAGAAATGTATAGGGGAGAAATCT
TGGGCTGAGTCAATGGATAGGTCCTAGGAGGTGGCTGGGGTTGAGAAATAGAAAGGCCTGGACACAATGTGATTGCTCAG
GCATACCAAGTTATAGCTCCAAGTTCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAGAAG
ACCTTGCTCCTTGGAATGCCCCAGATATTTTCCATACCCTCCTCGATATCCATGGAGAGCCTGGGGCTAGATATCTGG
CATATCCCTGGCATTGCTTCTCTCTTCTTCTTCTGTCATGTGTTGGTGGTGGTGTGGCAGGGGAATGTGGATAGGAGAT
GTCCTGGCAGATGCCTGCCAAAGTTTCATCCCACCCTCCCTGCTCATCGCCCCTGTTTTGAGGGCTGTGACTTGAGTTTT
TGTTTCCCATGTTCTCTATAGACTTGGGACCTTCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGG
AGAGGGAAGGAGGGAGGCAGGCATAGCATCTGAACCCAGTGTGGGGGCATTCACTAGGATCTTCAATCAACCCGGGCTCT
CCCCAACCCCCCAGATAACCTCCTCAGTTCCCTAGAGTCTCCTCTTGCTCTACTCAATCTACCCAGAGATGCCCTTAGC
ACACTCAGAGGGCAGGGACCATAGGACCCAGGTTCACACCCCATGTGAGGAGGGGAGGGGAGAGAGCCCCCTTCCCATC
ACCTGCTCGTCCCATTCAGCTTACCCTCCCAGTCAGCCAGAATCTGAGGGGAGGGGCCCCCAGAGAGCCCCCTTCCCATC
AGAAGACTGTTGACTGCTTTGCATTTTGGGCTCTTCTATATATTTTGTAAATAAGAACTATAACCAGATCTAATAAAACA
CAATGGCTATGCAAAAAAAAAAAAAAAAAAAAAA

MONKEY 9QS PROTEIN

MRGQGRKESLSDSRDLGSDYDQLTDSVEDEFELSTVCHRPEGLEQLQEQTKEFTRKELQVLYRGFKNECPSGIVNEENFKQ
IYSQFFPQGDSSSYATFLNFDTNHDGVSFEDFVAGLSVILRGTVDDRNLNWFNLYDLNKDGCITKEEMLDIMKSIYD
MMGKYTPALREEAPREHVENFFQKMDRNDKGVVTIEEFIESCQKDENIMRSMQLFDNVI

Fig. 13

SUBSTITUTE SHEET (RULE 26)

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RAT 9QC DNA (CD:208-966)

TGCTGCCCCAAGGCTCCTGCTCCTGCCCCAGGACTCTGAGGTGGGCCCTAAAACCCAGCGCTCTCTAAAGAAAAGCCTTGC
CAGCCCCCTACTCCCGGCCCCCAACCCAGCAGGTCGCTGCGCCGCCAGGGGGCGCTGTGTGAGCGCCCTATTCTGGCCAC
CCGGCGCCCCCTCCACGGGCCAGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAAGGCAGAAAGGAGAGTTTGTCC
GAATCCCAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCCTCCAGGGCCCAGTAAAAAGCCCTGAAGCAGCG
TTTCTCAAGCTGCTGCGGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAACAGCGTAGAGGATGAGTTTGAAT
TATCCACGGTGTGTACCCGACCTGAGGGCCTGGAACAACCTCCAGGAACAGACCAAGTTCACACGCAGAGAGCTGCAGGTC
CTGTACCGAGGCTTCAAGAACGAATGCCCCAGTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTTATTCTCAGTTCTT
TCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTCAGTTTTG
AGGACTTTGTGGCTGGTTTGTGCGGTGATTCTTCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTATATGAC
CTCAACAAGGACGGCTGTATCACAAGGAGGAAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAAGTACAC
ATACCCTGCCCTCCGGGAGGAGGCCCAAGAGAACACGTGGAGAGCTTCTTCAGAAGATGGACAGGAACAAGGACGGCG
TGGTGACCATCGAGGAATTCATCGAGTCTTGTCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTCACCCCTTCTC
AACTGATACCTAGTGCTGAGGACACCCCTGGTGTAGGGACCAAGTGGTTCTCCACCTTCTAGTCCCCTCTAGAAACCAC
ATTAGACAGAAGGTCTCCTGCTATGGTGCTTTCCCCATCCCTAATCTCTTAGATTTTCCCTCAAGACTCCCTTCTCAGAGA
ACACGCTCTGTCCATGTCCCCAGCTGGCTTCTCAGCCTAGCCTTTGAGGGCCCTGTGGGGAGGCGGGGACAAGAAAGCAG
AAAAGTCTTGGCCCCGAGCCAGTGGTGTAGGTCTTAGGAATTGGCTGGAGTGGAGGCCAGAAAGCCTGGGCAGATGATGAG
AGCCCAGCTGGGCTGTCACTGCAGGTTCCGGGGCCTACAGCCCTGGGTCAGCAGAGTATGAGTCCCAGACTTTCCAGAA
GGTCTTAGCAATGTCCCAGAAATTCACCGTACACTTCTCAGTGTCTTAGGAGGGCCCCGGGATCCAGATGTCTGGTTCAT
CCCTGAATCCTCTCCCTCCTTCTTGCTCGTATGGTGGGAGTGGTGGCCAGGGGAAGATGAGTGGTGTCCCGGATGATGCC
TGTC AAGGTCCCACCTCCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCTCCATGACCCCTATCTAGATGTAGAGGCA
TGGAGTGAGTCAGGGATTTCCCGAAGTTGAGTTTTACCACTCCTCCTAGTGGCTGCCTTAGGGGAATGGGAAGAACCAG
TGTGGGGGCACCCATTAGAATCTTTGCCCGGCTCCTCACAATGCCCTAGGGTCCCCTAGGGTACCCGCTCCCTCTGTTTA
GTCTACCCAGAGATGCTCCTGAGCTCACCTAGAGGGTAGGGACGGTAGGCTCCAGGTCCAACCTCTCCAGGTGAGCACCC
TGCCATGCTGCTGCTCCTCATTAACAAACCTGCTTGTCTCCTCCTGCGCCCCCTCTCAGTCAGCCAGGGTCTGAGGGGAA
GGGCCTCCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTTGCATTTTGGGCTCTTCTATCTATTTTGTAAATAAGA
CATCAGATCCAATAAAAACACACGGCTATGCACAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

RAT 9QC PROTEIN

MRGQGRKESLSESRDLGSDYDQLTGHPPGPSKKALKQRFLKLLPCCGPQALPSVSENSVEDEFELSTVCHRPEGLEQLQE
QTKFTRRELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGITD
DRLSWAFNLYDLNKDGCITKEEMLDIMKSIYDMMKYTYPALREEAPREHVESFFQKMDRNDGVVTTIEEFIESCQQDEN
IMRSMQLSPLLN

Fig. 14

SUBSTITUTE SHEET (RULE 26)

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RAT 8T (9Q SPLICE VARAIANT) DNA (MAY NOT BE FULL LENGTH, CD: 1-678)
ATGAACCACTGCCCTCGCAGGTGCCGGAGCCCGTTGGGGCAGGCAGCTCGATCTCTCTACCAGTTGGTAACTGGGTCGCT
GTCGCCAGACAGCGTAGAGGATGAGTTTGAATTATCCACGGTGTGTCACCGACCTGAGGGCCTGGAACAACCTCCAGGAAC
AGACCAAGTTCACACGCAGAGAGCTGCAGGTCTGTACCGAGGCTTCAAGAACGAATGCCCCAGTGGGATTGTCAACGAG
GAGAACTTCAAGCAGATTTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTT
TGACACCAACCACGATGGCTCTGTCTAGTTTGTGAGGACTTGTGGCTGGTTGTGGTGATTCTTCGGGGGACCATAGATG
ATAGACTGAGCTGGGCTTTCAACTTATATGACCTCAACAAGGACGGCTGTATCACAAGGAGGAAATGCTTGACATTATG
AAGTCCATCTATGACATGATGGGCAAGTACACATACCCTGCCCTCCGGGAGGAGGCCCCAAGAGAACACGTGGAGAGCTT
CTTCCAGAAGATGGACAGGAACAAGGACGGCGTGGTGACCATCGAGGAATTCATCGAGTCTTGTCAACAGGACGAGAACA
TCATGAGGTCCATGCAGCTCTTTGATAATGTCATCTAGCTCCCCAGGGAGAGGGGTTAGTGTGTCTAGGGTGACCAGGC
TGTAATCCTAGTCCAGACGAACCTAACCTCTCTCTCCAGGCTGTCTCATCTTACCTGTACCCTGGGGGCTGTAGGGA
TTCAATATCCTGGGGCTTCAGTAGTCCAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGTAGGCAAGCTAAATCTGG
GGGCTTCCCAACCCCGACAGCTCTCACCCCTTCTCAACTGATACCTAGTGCTGAGGACACCCCTGGTGTAGGGACCAAG
TGGTTCTCCACCTTCTAGTCCCACTCTAGAAAACCACATTAGACAGAAGGTCTCCTGCTATGGTGCTTTCCCCATCCCTAA
TCTCTTAGATTTTCTCAAGACTCCCTTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGGCTTCTCAGCCTAGCCTT
TGAGGGCCCTGTGGGGAGGCGGGGACAAGAAAGCAGAAAAGTCTTGGCCCCGAGCTAGTGGTTAGGTCTTAGGAATTGGC
TGGAGTGGAGGCCAGAAAGCCTGGGCAGATGATGAGAGCCCAGCTGGGCTGTCACTGCAGGTTCAGGGCCTACAGCCCT
GGGTCAGCAGAGTATGAGTTCCAGACTTTCCAGAAGGTCTTAGCAATGTCCCAGAAATTCACCATACACTTCTCAGTG
TCCCGGATGATGCCTGTCAAGGTCCACCTCCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCTCCATGACCCCTATC
TAGATGTAGAGGCATGGAGTGAGTCAGGGATTTCCCGAACTTGAGTTTACCCTCCTCCTAGTGGCTGCCTTAGGGGAA
TGGGAAGAACCCAGTGTGGGGGCACCCATTAGAATCTTTGCCCGGTTCTCACAATGCCCTAGGGTCCCCTAGGGTACCC
GCTCCCTCTGTTTAGTCTACCCAGAGATGCTCCTGAGCTCACCTAGAGGGTAGGGACGGTAGGCTCCAGGTCCAACCTCT
CCAGGTGAGCACCCCTGCCATGCTGCTGCTCCTCATTAACAAACCTGCTTGTCTCCTCCTGCGCCCCCTTCTCAGTCAGCCA
GGGTCTGAGGGGAAGGGCCTCCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTGCATTTTGGGCTCTTCTATCTAT
TTTGTAATAAAGACATCAGATCCAATAAAACACACGGCTATGCACAAAAAAAAAAAAAAAAAAAA

RAT 8T (9Q SPLICE VARAIANT) PROTEIN (MAY NOT BE FULL LENGTH)
MNHCPRRCRSPLGQAARSLYQLVTGSLSPDSVEDEFELSTVCHRPEGLEQLQEQTFRRELQVLYRGFKNECPSGIVNE
ENFKQIYSQFFPQGDSSNYATFLNAFDTHDGSVSFEDFVAGLSVILRGTIDRLSWAFNLYDLNKDGCITKEEMLDIM
KSIYDMMGKYTYPALREEAPREHVESFFQKMDRNKDGVTIEEFIESCQQDENIMRSMQLFDNVI

Fig. 15

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>human KChIP3 cds=1-7:
ATGCAGCCGGCTAAGGAAGTGACAAAGGCGTCGGACGGCAGCCTCCTGGGGGACCTCGGGC
ACACACCACTTAGCAAGAA
GGAGGGTATCAAGTGGCAGAGGCGAGGCTCAGCCGCCAGGCTTTGATGAGATGCTGCCTG
GTCAAGTGGATCCTGTCCA
GCACAGCCCCACAGGGCTCAGATAGCAGCGACAGTGAGCTGGAGCTGTCCACGGTGCGCCA
CCAGCCAGAGGGGCTGGAC
CAGCTGCAGGCCCAGACCAAGTTCACCAAGAAGGAGCTGCAGTCTCTCTACAGGGGCTTTA
AGAAATGAGTGTCCCACGGG
CCTGGTGGACGAAGACACCTTCAAACCTCATTTACGCGCAGTTCTTCCCTCAGGGAGATGCCA
CCACCTATGCACACTTCC
TCTTCAACGCCTTTGATGCGGACGGGAACGGGGCCATCCACTTTGAGGACTTTGTGGTTGGC
CTCTCCATCCTGCTGCGG
GGCACAGTCCACGAGAAGCTCAAGTGGGCCTTTAATCTCTACGACATTAACAAGGATGGCT
ACATCACCAAAGAGGAGAT
GCTGGCCATCATGAAGTCCATCTATGACATGATGGGCCGCCACACCTACCCCATCCTGCGGG
AGGACGCGCCGGCGGAGC
ACGTGGAGAGGTTCTTCGAGAAAATGGACCGGAACCAGGATGGGGTAGTGACCATTGAAGA
GTTCTTGGAGGCCTGTCAG
AAGGATGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAATGTCATCTAGgacacgtccaaaggagt
gcatggccacag
ccacctccaccccccaagaaacctccatcctgccaggagcagcctccaagaaacttttaaaaaatagatttgcaaaaagtg
aacagattgctacacacacacacacacacacacacacacacacacacagccattcatctgggctggcagaggggac
agagttcagggaggggctgagctctggctaggggcccaggtccaggagccccagccagccctcccaggccagcgaggcgag
gctgcctctgggtgagtggtgacagagcaggtctgcaggccaccagctgctggatgtcaccaagaaggggctcgagtgc
ccctgcaggggaggggtccaatctccggtgtgagccaccctcgctcccgttctccattctgctttcttgccacacagtgggc
cggccccaggtccccctggtctcctccccgtagccactctctgcccactacctatgcttctagaaagccccctcacctcag
gacccagagggaccagctggggggcaggggggagagggggtaatggaggccaagcctgcagctttctggaaattcttcc
ctgggggtcccaggatccccctgctactccactgacctggaagagctgggtaccaggccaccactgtggggcaagcctga
gtggtgagggggccactgggccccattctccctccatggcaggaaggcgggggatttcaagtttagggattgggtcgtggt
ggagaatctgagggcactctctgccagctccacaggggtgggatgagcctctccttgccccagctcctggttcagtgggaat
gcagtgggtggggctgtacacaccctccagcacagactgttccctccaaggtcctcttaggtcccgggaggaacgtggtt
cagagactggcagccagggagcccggggcagagctcagaggagtctgggaagggcggtgtccctcctcttctgtagtgc
ccctcccatggcccagcagcttaggtgagccccctctcctgaagcagtgctgccgtccctctgccttgcaaaaaagca
aagcattccttagcagctcaggcgcagccctagtgggagcccagcacactgcttctcgaggccaggccctcctgctggc
tgaggcttggggccagtagcccaatatggtggccctggggaagaggccttgggggtctgctctgtgcctgggatcagtg
gggccccaaagcccagccggctgaccaacattcaaaagcacaaaccctggggactctgcttgggtgtccccctccatctg
gggatggagaatgccagcccaaagctggagccaatggtgagggctgagagggctgtggctgggtgggtcagcagaaacccc
caggaggagagagatgctgctcccgcctgattggggcctcaccagaaggaacccggtcccaggccgcatggccccctcca
ggaacattcccacataatacattccatcacagccagcccagctccactcagggctggccccggggagtccccgtgtgcccc
aagaggctagccccagggtgagcagggccctcagaggaaaggcagtatggcggaggccatggggggccctcggcattcac
acacagcctggcctcccctgcggagctgcatggacgcctggctccaggctccaggctgactgggggcctctgcctccagg
aggcatcagctttccctggctcagggatcttctccctcccctcaccgctgccagccctcccagctgggtgtcactctg
cctctaaggccaaggcctcaggagagcatcaccaccacacccctgccggccttggccttggggccagactgggtgcacag
ccaaccaggaggggtctgcctcccacgctgggacacagaccggccgcatgtctgcatggcagaagcgtctcccaggcc
acggcctgggaggggtggttctgttctcagcatccactaatattcagtcctgtatattttaataaaataaacttgacaaa
ggaaaaaaaaaaaaaaaaaattcctgcggccgcgttctcca

Fig. 16

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>human KChip3
MQPAKEVTKASDGSLLGDLGHTPLSKKEGIKWQRPRLSRQALMRCCLVKWILSSTAPQGSDDSD
SELELSTVRHQPEGLD
QLQAQTKFTKKELQSLYRGFKNECPTGLVDEDTFKLIYAQFFPQGDATTYAHFLFNAFDADGNG
AIHFEDFVVGLSILLR
GTVHEKWKWAFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPAEHVERFFEKMD
RNQDGVVTIEEFLEACQ
KDENIMSSMQLFENVI

Fig.16 Continued

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RAT P19 DNA (FIRST PASS, PARTIAL; CD:1-330)

TTTGAGGACTTTGTGGTTGGGCTCTCCATCCTGCTTCGAGGGACCGTCCATGAGAAGCTCAAGTGGGCCTTCAATCTCTA
CGACATCAACAAGGACGGTTACATCACCAAAGAGGAGATGCTGGCCATCATGAAGTCCATCTACGACATGATGGGCGGCC
ACACCTACCCTATCCTGCGGGAGGACGCACCTCTGGAGCATGTGGAGAGGTTCTTCCAGAAAATGGACAGGAACCAGGAT
GGAGTAGTGACTATTGATGAATTTCTGGAGACTTGTGAGAAGGACGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAA
CGTCATCTAGGACATGTAGGAGGGGACCCTGGGTGGCCATGGGTTCTCAACCCAGAGAAGCCTCAATCCTGACAGGAGAA
GCCTCTATGAGAAACATTTTTCTAATATATTTGCAAAAAGTG

RAT P19 PROTEIN (PARTIAL)

FEDFVVGLSILLRGTVHEKLKWFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPLEHVERFFQKMDRNQD
GVVTIDEFLETCQKDENIMSSMQLFENVI

Fig. 17

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MOUSE P19 DNA (CD: 49-819)

CGGGCTGCAAAGCGGGAAGSTTAGTGACGGTCCCTTTTCAGCAGCAGAGATGCAGAGGACCAAGGAAGCCGTGAAGGCATC
AGATGGCAACCTCCTGGGAGATCCTGGGCGCATACCACTGAGCAAGAGGGAAAGCATCAAGTGGCAAAGGCCACGGTTCA
CCCGCCAGGCCCTGATGCGTTGCTGCTTAATCAAGTGGATCCTGTCCAGTGCTGCCCCACAAGGCTCAGACAGCAGTGAC
AGTGAAGTGGAGTTATCCACGGTGCGCCATCAGCCAGAGGGCTTGGACCAGCTACAAGCTCAGACCAAGTTCACCAAGAA
GGAGCTGCAGTCCCTTTACCGAGGCTTCAAGAATGAGTGTCCCACAGGCCTGGTGGATGAAGACACCTTCAAACTCATTT
ATTCCCAGTTCTTCCCTCAGGGAGATGCCACCACCTATGCACACTTCCCTCTTCAATGCCCTTTGATGCTGATGGGAACGGG
GCCATCCACTTTGAGGACTTTGTGGTTGGGCTCTCCATCCTGCTTCGAGGGACGGTCCATGAGAAGCTCAAGTGGGCCTT
CAATCTCTATGACATTAACAAGGATGGTTGCATCACCAGGAGGAGATGCTGGCCATCATGAAGTCCATCTACGACATGA
TGGGCGCCACACCTACCCATCCTGCGGGAGGATGCACCCCTGGAGCATGTGGAGAGGTTCTTTCAGAAAAATGGACAGG
AACCAGGATGGAGTGGTGACCATTTGATGTATTTCTGGAGACTTGTGAGAAGGATGAGAACATCATGAAGTCCATGCAGCT
GTTTGAGAACGTCATCTAGGACATGTGGGAGGGGACCCAGTGGTCATTGCTTCTCAACCCAGAGSAGCCTCAATCCTGA
CAGGAGAAGCCTCTATGAGAAACATTTTCTAATATATTTGCAAAAAGTGAGCAGTTTACTTCCAAGACACAGCCACCGT
CACACACAGACACAGACATACAGACACACACACACACACACATGGTTCCCTCTGGCTTGGCCAAGGAAGTGGCAGCC
AGAAGGCACCCCCGCCTATTCCTAGGTCAATAAAAAAGGCTGCCCTCTGGGATGGCCAGCCCTGGCTAGATGTTACCCACA
AGGAACTCAGAGATCGAGAGGACCAGGTCTACAAAGCTAAGGTCCCTGTGTCTTTTCTACCACTCGGGAGATCAAACCTAC
TCCCTGCCTATGGACCCATGCTCTTAGGAAGCTCCCAGAACTCCAAGGGGACAAAGAGGGGAGAGGTCTATAGGAAGAA
ATGGTTTTTGAAGCTGGGCTTGCAGCCTTATGCTAATGATCACCTGGGGTCCCTGGAACCCGAGTGCCAGGCTACCTACTA
TGCCGTGAGCTTAGATAGTGAGGGGCCATTGGACTAAGACCTCCTGTAAGAGTGGGGCAGGATTGAGGTTTTTGGAGAAA
CTGAGGAAACAATTTGTCCATACCACTGGGTGAAGACTGCTGGCCAGTGGGAATGTGGCTGGTGGAGATTTCCCAACTTC
CAGCACCAGGATGGCCTCTCCAAGGTCTCTTTGATTCCCTGGGGAGATCACCTGGCTCATAGACTGACAACCAGGGAAC
TGGGCTGAAAATGGGAGGTCTGGTAGGGGGCATCCCCCTCCTTTTCCCTGGCCACTTGCCACCCAGTTCCTTAACACAGTG
GATCGGCCACACCTCTGTGGCTGCCCTTGAACAGACTCATCCCGACCAAGACAAAAAGCACTAACTCCTAGCAGCTCAG
GCCAAGCCCAACAAGGAAGGCCTGGGTCCCTGCAGCCCTGATTCAAGTGGCCGAGGAAGACGCTCAGACATCCATCCTGTA
CCTCGGAGCCTTGGGGGTCTCACAGCCCTTTCCAGCCAGCTCGCCAACATTCTAAAGCACAAACCTGCGGATTCTGCT
TGCTTGGGCTGCGCCCTGGGGATTGAAGGCCACTGTTAACCCTAAGCTGGAGCTAGCCCTGAGGGCTGGGGACCTGTGAC
CAGGCAACAGGTGAGCAGACCCTCAGGAGGAGAGAGAGCTGTTCCCTGCCTCCCCAGGCCTCGCCAGAAGGAACAGTGT
CCAAGAAGCATGTTTCTGGAGGAACATCCCCACAAAAGTACATTCCATCATCTGAAGCCCGGTCTCTGCTCAGGCCTGC
CTCTGAAAGTCCACGTGTGTTCCCCAGAAGGCCAGCCCCAAGATAAGGGAGGTCCCTTAGAGGAAGGACAGGGTGACAACA
CCCCATACACAGGTGGACCCCCCTCTGAGGACTGTACTGACCCCATCTCCATCCTGACCGGGGCTTCCCTTTACCCGA
TCTACAGACCACAGTTCTCCCTGGCTCAGGGACCCCTGTCCCCAGTCTGACTCTTCCCATCGAGGTCCCTGTCTTGT
GAAAAGCCAAGGCCACGGGAAAAGGCCACCACTCTAACCTGCTGCATCCCTTAGCCTCTGGCTGCACGCCCCAACCTGGAG
GGGTCTGTCCCTTTGCAGGGACACAGACTGGCCGCATGTCCGCATGGCAGAAGCGTCTCCCTTGGGTGCAGCCTGGAAG
GGTGGTTTTCTGTCTCAGCGCCACCAATATTCAGTCCTATATATTTTAATAAAAGAACTTGACAAAGGAAAAAAAAA
AAAA

Fig. 18

SUBSTITUTE SHEET (RULE 26)

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>AI 352454 (partial) cds = 1-339
CACGAGGTGGAAAGCATTTCGGCTCAGCTGGAGGAGGCCAGCTCTACAGGCGGTTTCCTGT
ACGCTCAGAACAGCACCAA
GCGCAGCATTAAAGAGCGGCTCATGAAGCTCTTGCCCTGCTCAGCTGCCAAAACGTCGTCTC
CTGCTATTCAAAACAGCG
TGGAAGATGAACTGGAGATGGCCACCGTCAGGCATCGGCCCGAAGCCCTTGAGCTTCTGGA
AGCCCAGAGCAAATTTACC
AAGAAAGAGCTTCAGATCCTTTACAGAGGATTTAAGAACGTAAGAACTTTCTTTTGACTTT
ACCTTCACACAATTCCCA
GAGGAGCATTGAGAAATGAgaggaaaaggggaaaatatcccattctatgagaagcccatcatatgtatatttcatact
gaccttcccagataggaatataatcagtatctgtggactttgaatctctgtggcacacccatgctggcatactgtaatt
gcccattaaacaaanagtttttgagaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
>AI352454
HEVESISAQLEEASSTGGFLYAQNSTKRSIKERLMKLLPCSAKTSSPAIQNSVEDELEMATVRHR
PEALELLEAQSKFT
KKELQILYRGFKNVRTFFLTLP SHNSQRSIEK

Fig. 19

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P193 (AA349365) DNA (CD:2-127,patial)

TGAAAGGTTCTTCGAGAAAATGGACCGGAACCAGGATGGGGTAGTGACCATTGAAGAGTTCCTGGAGG
CTGTCAGAAGGATGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAATGTCATCTAGGACACGTCCAAA
GGAGTGATGGCCACAGCCACCTCCACCCCCAAGAAACCTCCATCCTGCCAGGAGCAGCCTCCAAGAAA
CTTTTAAAAAATAGATTTGCAAAAAGTGAACAGATTGCTACACACACACACACACACACACACACAC
ACACACACACAGCCATTTCATCTGGGCTGGCAGAGGGGACAGAGTTCAGGGAGGGGCTGAGTCTGGCTAG
GGGCCGAGTCCAGGAGCCCCAGCCAGCCCTTCCCAGGCCAGCGAGGCGAGGCTGCCTCTGGGTGAGTGG
CTGACAGAGCAGGTCTGCAGGCCACCAGCTGCTGGATGTCACCAAGAAGGGGCTCGAGTGCCCTGCAG
GGGAGGGTCCAATCTCCGGTGTGAGCCACCTCGTCCCGTTCTCCATTCTGCTTTCTTGCCACACAGTGGG
CCGGCCCCAGGCTCCCCTGGTCTCCTCCCCGTAGCCACTCTCTGCCACTACCTATGCTTCTAGAAAGCCC
CTCACCTCAGGACCCCAGAGGGACCAGCTGGGGGGCAGGGGGGAGAGGGGGTAATGGAGGCCAAGCCT
GCAGCTTCTGGAATTTCTTCCCTGGGGGTCCCAGGATCCCCTGCTACTCCACTNACCTGGAAGAGCTGG
GTACCAGGCCACCCACTGTGGGGCAAGCCTGAGTGGTGAGGGGCCACTGGGCCCCATTCTCCCTCCATGG
CAGGAAGGCGGGGATTTCAAGTTTAGGGATTGGGTGCTGGTGGAGAATCTGAGGGCACTCTCTGCCAG
CTCCACAGGGTGGGATGAGCCTCTCCTTGCCCCAGTCCTGGTTTCAGTGGGAATGCAGTGGGTGGGGCIGT
ACACACCCTCCAGCACAGACTGTTCCCTCCAAGGTCTCTTAGGTCCCGGGAGGAACGTGGTTTCAGAGAC
TGGCAGCCAGGGAGCCCGGGGCAGAGCTCAGAGGAGTCTGGGAAGGGGCGTGTCCCTCCTCTTCTGTA
GTGCCCCCTCCCATGGCCCAGCAGCTTGCTGAGCCCCCTCTCCTGAAGCAGTGTGCGCGTCCCTCTGCCTT
GCACAAAAGCACAAGCATTCTTAGCAGCTCAGGCGCAGCCCTAGTGGGAGCCCAGCACACTGCTTCT
CGGAGGCCAGGCCCTCCTGCTGGCTGAGGCTTGGGCCCAGTAGCCCCAATATGGTGGCCCTGGGGAAGA
GGCCTTGGGGGTCTGCTCTGTGCTGGGATCAGTGGGGCCCCAAGGCCAGCCGGCTGACCAACATTCA
AAAGCACAAACCTGGGGACTCTGCTTGGCTGTCCCCTCCATCTGGGGATGGAGAATGCCAGCCCAAAG
CTGGAGCCAATGGTGAGGGCTGAGAGGGCTGTGGCTGGGTGGTCAGCAGAAAACCCAGGAGGAGAGA
GATGCTGCTCCCGCCTGATTGGGGCCTCACCCAGAAGGAACCCGGTCCCAGGCCGATGGCCCCCTCCAGG
AACATTCCCACATAATACATTCCATCACAGCCAGCCAGCTCCACTCAGGGCTGGCCCGGGGAGTCCCCG
TGTGCCCCAAGAGGCTAGCCCCAGGGTGAGCAGGGCCCTCAGAGGAAAGGCAGTATGGCGGAGGCCATG
GGGCCCCCTCGGCATTACACACAGCCTGGCCTCCCCTGCGGAGCTGCATGGACGCCTGGCTCCAGGCTC
CAGGCTGACTGGGGGCTCTGCCTCCAGGAGGGCATCAGCTTTCCCTGGCTCAGGGATCTTCTCCCTCCC
CTCACCCGCTGCCCAGCCCTCCCAGCTGGTGTCACTCTGCCTCTAAGGCCAAGGCCTCAGGAGAGCATCA
CCACCACACCCCTGCCGGCCTTGGCCTTGGGGCCAGACTGGCTGCACAGCCCAACCAGGAGGGGTCTGC
CTCCACGCTGGGACACAGACCGCCGCATGTCTGCATGGCAGAAGCGTCTCCCTTGGCCACGGCCTGGG
AGGGTGGTTCCTGTTCTCAGCATCCACTAATATTTCAGTCTGTATATTTTAAATAAAATAAACTTGACAAAG
GAAAAAAAAAAAAAAAAAAAA

P193 PROTEIN (PARTIAL)

ERFFEKMDRNQDGVVTIEEFLEACQKDENIMSSMQLFENVI

Fig. 20

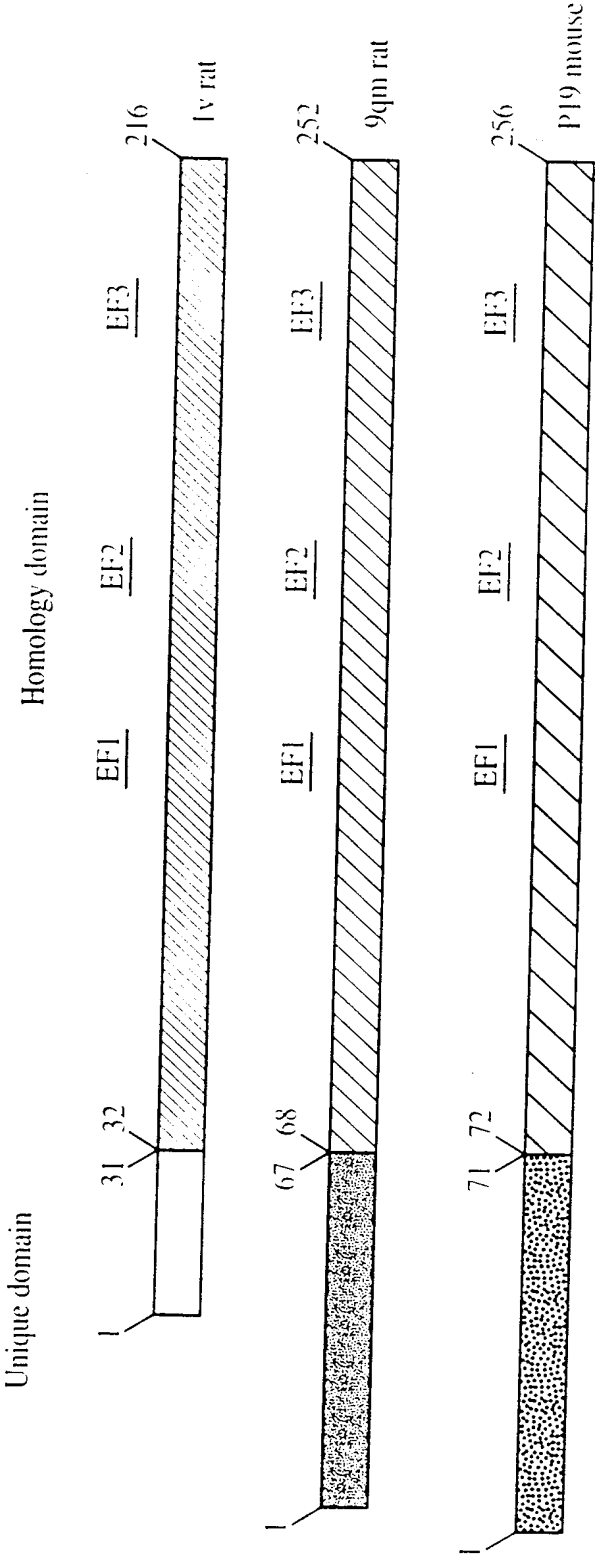


Fig. 21

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ACTCAGCGNGGGTGGGACAGGAGGACCCAANCCGGTCCANATTTTTTCCCANAAAGCATGGCTTNGATGCTTGAGGNG
CGGGCGGAAGGGAGGCAAGGCCCTGAGACTGAACTTCTAGCTGGAGGTTCTGGGGCGGGGCCAGAACGRAAGTGGCG
CCTGTAGACTGTCAGTTTCGTTCCATGTTTTTTATTTGTGCACTGGGAAAGAAGTCTTCCCTCCCATCACATGAGCC
ACGTGGTGAGTCTCTGGAGGCTTGAAGATTATCCCCCTCCCTGGGAGTCTTGGGCCATGGAGGGTGGGGCGGTGA
ACGGAAGGGGATTTGTCTCTGCCCTCAGCCTGGTGCCTCTCCTTCCAGGAATGTCCCAGCGGAATTGTCAATGAG
GAGAACTTCAAGCAGATTTACTCCCAGTTCTTTCTCAAGGAGGTGAGGGGACAAGGCCAAGGGGAAGCAGTTGTC
CTTCTCTAGGCTGAGGGAGGGAGGGATTCTGGAGGAGCTGGGAATGCCAAGGTGATGGGGGTATGGGGAGCTCCTT
AGAGGGAGGAAGTCCCTCTCTGTGTGGAAGCCAACCTTCTCCACACTCACCTGCAGACTCCAGCACCTATGCCACTT
TTCTCTTCAATGCCTTTTGACACCAACCATGATGGCTCGGTCACTTTTGGGTGAGCTGGGCGAGGTGGGCCAGGGAA
GCCTGTTTCTGGAGTTTCAGGGCCAGGATCTCCAGGCCAAACCCAGAGAAGGAGTTGGGTGAAGAGKACCCGAGGAC
ACAGCTCCCTNCTGCCTTCTTCCCAGGACTTTGTGGCTGGTTTGYCCGTGATTCTTCGGGGAAGTGTAGATGACAGG
CTTAATTGGGCCTTCAACCTGTATGACCTTAACAAGGACGGCTGCATCACCAGGAGGTGCAGGGCAACTGAAGGGC
TGGGGGTCTGTGGCGGTGATGGGGGTGGCGTGCAGAGGTGATGGGAGGGAAATATGACCCACATATGCCACAAGC
AATGGGATCAAGGGAGGCTGGAGGCTCTGAGGAAGGATCCTCTCTCTCTTGGCCTAACAGGAAATGCTTGACATCA
TGAAGTCCATCTATGACATGATGGGCAAGTACAGTACCCTGCAGTCCGGGAGGAGGCCCAAGAAACACGTGGAG
AGCTTCTTCCAGGTACTTGGGAGTGGGTATGGCTGGAGGGCCCTGGAGTGAAGGGAAGAAGGCCAAGAACCAGAGG
GAACTCACCTGACTTCTGTCTGCCTCTCTCTTGCCATCCCTCCTGTTCTCCCTGCCTGACCACCTTCTTGCAGAAGA
TGGACAGAAACAAGGATGGTGTGGTGACCATGAGGAATTCATTGAGTCTTGTCAAAAGGTACAGCTCCCTGCCCTC
TACATTACCTTGACCTGGACTCAGGCCTGATTTAGTAATGCAGGGAAGGCTTCTTTGGGAAGAATACCACCTTCCC
ACCTCACCCCATATTTCAATCCTATTCCTTTGTGGGAGGCTTACCCCTTCCCTACCTCAGGTCTCTCTGGGCATCT
CCTTCTCTGTGCTTTTGAATGTCCCCGTCTGTGACTCAAGTGTCCCTCTCACTGTCTCTGATAAAGCTCCTTCTCT
TTCTCTCTCTCAATCTGCCTCGCTCACATCATGGCCACAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGAC
AATGTCTATAGCCCCCAGGAGAGGGGGTCACTGTTTCTGGGGGGACCATGCTCTAACCTTAGTCCAGGCGGACCT
CACCTTCTCTTCCCAGGTCTATCCTCATCTACGCCTCCCTGGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTGAG
TAGTCCAGATCTCTGGAGCTGAAGGGGCCAGAGAGTGGGCAGAGTGCATCTCGGGGGGTGTTCCCAACTCCCACCAG
CTCTCACCCCTTCCCTGCCTGACACCCAGTGTGAGAGTGGCCCTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTA
CCCCACTCTAGAAACACACTAGACAGATGTCTCTGTATGGTGTCTCCCCATCCCTGACCTCATAACATTTCC
CCTAAGACTCCCTCTCAGAGAGAATGCTCCATTCTTGGCACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTG
TGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCCTGAGTCAATGGATAGGTCCATAGAGGTGGCTGGGGTT
GAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCAGGTTATAGCTCCAAGTTCACAGGTCTGCTAC
CACAGGCCATCAAAATATAAGTTTCCAGGCTTTCAGAGAAGACCTTGTCTCCTTAGAAATGCCCCAGAAATTTCCAC
ACCCTCCTCGGTATCCATGGAGAGCCTGGGGCCAGATATCTGGCTCATCTCTGGCATGCTTCTCTCCTTCTTTCC
TGCATGTGTTGGTGGTGGTGTGGTGGGGGAATGTGGATGGGGGATGTCTGGCTGATGCCTGCCAAAATTTTCATCC
CACCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACTTGAGTTTTTGTCTTCCCATGTTCTCTATAGACTTGGG
ACCTTCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAAGGAGGGAGGCAGGCATA
GCATCTGAACCCAGTGTGGGGCATTCACTAGAATCTTCAATCAACCTGGGCTCTCCCCACCCACCCAGATAACC
TCCTCAGKTCCTAGGGTCTCTCTYGCTTGAATCAATCTACCCAGAGATGCCCCCTTAGCACACCTAGAGGGCAGGG
ACCATAGGACCCAGGTTCCAACCCATTGTGACACCCAGCCATGCGGCCACCCCTTAGCACACCTGCTCGTCCCA
TTTAGCTTACCTCCCAGTTGGCCAGAATCTGAGGGGAGAGCCCCCAGAGAGCCCCCTTCCCCATCAGAAGACTGTT
GACTGCTTTGCATTTTGGGCTCTTCTATATATTTTGTAAAGTAAGAAATATACCAGATC : TAATAAAACACAATGGC
TATGCACAGGCTGCCGTCTCTGCCTTTTGTCCCTCCACCTACAAATACTACACAACCCCTAACGAATGCACCTGCA
GCCTTTTGTAGATCCCCAAGAAAGTGGCTTTCTTTTCCATAGTTGGCCATACCTTGGCATGAGACTGAGACACAGGCTC
TGAATGGTTGGAAACCCACCCACCTCAGGCCCCCACATGAATCTCCCTCCACACAGCCTGAGAGGAGACAAGGA
AGGAAGGACAGGACACTGATGTCCGAAGACTGTGCCAAGCAAGCTGTTTTTTAGCTGACATTCTTACAAGTTGAAT
CACAGATTTCTAATTTACAGACTTTTTTAGTTAATCTCAAAGTGCTTTCTTTTGGGGGCCCTCCTTAAAGTTCYTTCT
TTTTTTTTTTTTTTT

Fig. 22 Continued

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>monkey KChIP4 cds = 265

gtcgacccacgcgtccggtgcgctgtggagcggggggagccccgccagccaaatgccaggatcagcatgagaggctgg
acttttagtccaggtctgtcctcaccgccgggggaccgcccggctttgcaggggtgcagctgcgaggaactgctcacttttttc
cccttgcaagtctttgttccaagcctgacgttgctacgattctgttaattaactccctccactccaaaggggtctggagggc
tgggatgctctgccagctcagaggATGTTGACTCTGGAGTGGGAGTCCGAAGGACTGCAAACAGTGGGTA
TTGTTGTGAT
TATATGTGCATCTCTGAAGCTGCTTCATTTGCTGGGACTGATTGATTTTTTCGGAAGACAGCGT
GGAAGATGAACTGGAGA
TGGCCACTGTCAGGCATCGGCCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAATTTACC
AAGAAAGAGCTTCAGATC
CTTIACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTGTTAATGAAGAAACCTTCAAAGA
GATTTACTCGCAGTTCTT
TCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACA
ATGGAGCTGTGAGTTTCG
AGGATTTTCATCAAAGGTCTTTCCATTTTGCTCCGGGGGACAGTACAAGAAAACTCAATTGG
GCATTTAATCTGTATGAT
ATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAAGCAATATACG
ACATGATGGGTAAATGTAC
ATATCCTGTCCTCAAAGAAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGAAAATGG
ACAAAAATAAAGATGGGG
TTGTTACCATAGATGAGTTCATTGAAAGCTGCCAAAAAGATGAAAACATAATGCGCTCCATG
CAGCTCTTTGAAAATGTG
ATTTAACTtgcactagatcctgaatccaacagacaaatgtgaactattctaccacccttaaagtcggagctaccactt
ttagcatagattgctcagcttgacactgaagcatattatgcaaacaagctttgttttaataaagcaatccccaaaaga
tttgagtttctcagttataaatttgcaccccttccataatgccactgagttcatgggatgttctaactcatttcatactc
tgtgaatattcaaaaagtaataagaatctggcatatagttttattgattcccttagccatgggattattgaggctttcacata
tcagtgatttttaaaataaccagtgtttttgctctcatttgtatgtattcagtcctaggattttgaatgggttttctaataat
actgacatctgcatttaatttccagaaattaaatttatttcatgtctgaatgctgtaattccatttatatactttaagt
aaacaaataagattactacaatttaaacacatagttccagtttctatggccttcccttcccaccttctattataaattaat
tttatctgggtatttttaaacatttaaaaatttatcatcagatcagcatatgcctaattatgcctaataaacttaata
agcatttaattttccatcatacattatagccaaggcctatatataataattttggatttgtttaattcttacaggct
gttttccattgtatcatcaagtgaagttcaagacggcatcaaaacaaaacaggatgtttacagacatatgcaaaggggtc
aggatatctatcctccagtatatgttaatgcttaataacaagtaatcctaacagcattaaaggccaaatctgtcctctt
cccctgacttccctacagcatgtttatattacaagccattcagggacaaaagaaaccttgactacccactgtctactagg
aacaacaaaacagcaagcaaaattcactttgaaagcaccagtggttccattacattgacaactactaccaagattcagta
gaaaataagtgctcaacaactaatccagattacaatatgatttagtgcatcataaaattccaacaattcagattattttt
aatcatctcagccacaactgtaaagttgccacattactaaagacacacacatcgctccctgttttgtagaaatatcacaaa
gaccaagaggctacagaaggaggaaatttgcaactgtctttgcaacaataaatcaggtatctattctggtgtagagatag
gatgttgaaagctgccctgctatcaccagtgtagaaattaagagtagtacaatacatgtacactgaaatttgccatcgcg
tgtttggtgaaactcaatgtgcacattttgtattttcaaaaagaaaaataaaagcaaaataaaatgttwawaamwmwaaa
aaaaaaaaaaaaa

>monkey KChIP4

MLTLEWESEGLQTVGIVVVICASLKLHLLGLIDFSEDSVEDELEMATVRHRPEALELLEAQSKFT
KKELQILYRGFKNE
CPSGVVNEETFKEIYSQFFPQGDSTTYAHFLFNAFDTDHNGAVSFEDFIKGLSILLRGTVQEKLNW
AFNLYDINKDGYIT
KEEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETFFQKMDKNKDGVVTTIDEFIESCQKDNIM
RSMQLFENVVI

Fig. 23

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>monkey KChIP4 C terminal splice variant cds = 265-966
gtcgacccacgcgtccgggtgcgctgtggttgcggggggggagccccgccagccaaatgccaggatcagcatgagaggctgg
acttttagtccaggtctgtcctcaccgccggggaccgcccggctttgcagggtgcagctgcgaggaactgctcacttttttc
cccttgcaagtctttgttccaagcctgacgttgctacgattctgtgaattaactccctccactccaaaggggtctggaggc
tgggatgctctgccagctcagaggATGTTGACTCTGGAGTGGGAGTCCGAAGGACTGCAAACAGTGGGTA
TTGTTGTGAT
TATATGTGCATCTCTGAAGCTGCTTCATTTGCTGGGACTGATTGATTTTTTCGGAAGACAGCGT
GGAAGATGAACTGGAGA
TGGCCACTGTCAGGCATCGGCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAATTTACC
AAGAAAGAGCTTCAGATC
CTTTACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTGTTAATGAAGAAACCTTCAAAGA
GATTTACTCGCAGTTCTT
TCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACA
ATGGAGCTGTGAGTTTCG
AGGATTTTCATCAAAGGTCTTTCCATTTTGCTCCGGGGGACAGTACAAGAAAACTCAATTGG
GCATTTAATCTGTATGAT
ATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAAGCAATATACG
ACATGATGGGTAAATGTAC
ATATCCTGTCTCAAAGAAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGGCTGTTT
TCCATTGTATCATCAAGT
GGAAGTTCAAGACGGCATCAAACAAAACAAGGATGTTTACAGACATATGCAAAGGGTCAGG
ATATCTATCTCCAGTATA
TGTTAATgcttaataacaagtaatcctaacagcattaaaggccaaatctgtcctctttccctgacttccttacagcatg
tttatattacaagccattcagggacaaagaaaccttgactacccactgtctactaggaacaaacaaacagcaagcaaaa
ttcactttgaaagcaccagtggttccattacattgacaactactaccaagattcagtagaaaataagtgtcaacaacta
atccagattacaatatgatttagtgcataaaaaattccaacaattcagattatttttaatcatctcagccacaactgta
aagttgccacattactaaagacacacacatcgctccctgttttgtagaaatatcacaaagaccaagaggctacagaaggag
gaaatttgcaactgtctttgcaacaataaatcaggtatctattctggtgtagagataggatgttgaaagctgccctgcta
tcaccagtgtagaaattaagagtagtacaatacatgtacactgaaatttgccatcgcggtgtttgtgtaaactcaatgtgc
acattttgtattttcaaaaagaaaaataaaaagcaaaaataaaaatggtwawaamwmwaaaaaaaaaaaaaaaaaaaa

>monkey KChIP4 C terminal splice variant
MLTLEWESEGLQTVGIVVIICASLKLHLLGLIDFSEDSVEDELEMATVHRPEALELLEAQSKFT
KKELQILYRGFKNE
CPSGVVNEETFKEIYSQFFPQGDSTTYAHFLFNAFDTDHNGAVSFEDFIKGLSILLRGTVQEKLNW
AFNLYDINKDGYIT
KEEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETFFQAVFHCIKWKFKTASNKTRMFTDICK
GSGYLSSSIC

Fig. 24

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```

KChIP1_1v -----MGAVMGTF-----SSLQTKQ----RKP-----
KChIP2_9q1 MRGQGRKESLSDSRDL DGSYDQLTGHPPGP TKKALKQRF LKLLPCCGPQALPSVSETLAA
KChIP3_p19 --MQPAKEVTKAS---DGSLLGDLGH---TPLSKKEGLKWQRPRLSRQALMRCCLVKWI
KChIP4_352 ---MLTLEWESEGLQTVGIVVITCAS---LKLHLHLGLIDFSE-----
KChIP4_231 ---MLTLEWESEGLQTVGIVVITCAS---LKLHLHLGLIDFSE-----
hsncspara ----HEVESISAQLEEASSTGGFLYAQN-STKRSIKERLMKLLPCS-----

KChIP1_1v -----SKDKIEDELEMTMVCHRPEGLEOLEAOTNFTKRELQVLYRGFKNECPS
KChIP2_9q1 PASLRPHRPRLDPDSVDDEFELSTVCHRPEGLEQLQEOTKFTRKELQVLYRGFKNECPS
KChIP3_p19 LSSTAPQ-----GSDSSDSELELSTVRHOPEGLDQLQAOTKFTKKELQSLYRGFKNECPT
KChIP4_352 -----DSVEDELEMATVRHRPEALELLEAQSKFTKKELQILYRGFKNECPS
KChIP4_231 -----DSVEDELEMATVRHRPEALELLEAQSKFTKKELQILYRGFKNECPS
hsncspara -AAKTSSP---AIQNSVEDELEMATVRHRPEALELLEAQSKFTKKELQILYRGFKNVRTF

KChIP1_1v GVVNEDTEFKQIYAQFFPHGDASTYAHYLFNAFDTTQTGSKVFEDFVTALSILLRGTVHEK
KChIP2_9q1 GIVNEENFKQIYSQFFPQGDSTTYATFLNAFDTNHDSVSFEDFVAGLSVILRGTVDDR
KChIP3_p19 GLVDEDETEKLIYAQFFPQGDATTYAHFLNAFDADGNGAIFEDFVGLSILLRGTVHEK
KChIP4_352 GVVNEETEKEIYSQFFPQGDSTTYAHFLNAFDTDHNGAVSFEDFVKGLSILLRGTVOEK
KChIP4_231 GVVNEETEKEIYSQFFPQGDSTTYAHFLNAFDTDHNGAVSFEDFVKGLSILLRGTVOEK
hsncspara FTLPSHNSQRSIEK-----

KChIP1_1v LRWTFNLYDINKDGYLNKEEMMDIVKAIYDMMGKYTYPVLKEDTPROHVDVFFQKMD---
KChIP2_9q1 LNWAFNLYDINKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMD---
KChIP3_p19 LKWFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPAEHVERFFQKMD---
KChIP4_352 LNWAFNLYDINKDGYITKEEMLDIMKAIYDMMGKCTYPVLKEDAPROHVETFFQKMD---
KChIP4_231 LNWAFNLYDINKDGYITKEEMLDIMKAIYDMMGKCTYPVLKEDAPROHVETFFQAVFHCI
hsncspara -----

KChIP1_1v ---KNKDGIVTLDEEFLESCQEDDNIMRSLQLFQNVN
KChIP2_9q1 ---RNKDGIVTIEEFLESCQKDNIMRSMQLFDNVI
KChIP3_p19 ---RNQDGVVTIEEFLEACQKDNIMSSMQLFENVL
KChIP4_352 ---KNKDGIVTIDEFLESCQKDNIMRSMQLFENVL
KChIP4_231 IKWKFKTASNKTRMFTDICKGSGYLSSSIC-----
hsncspara -----

```

Fig. 25

Rat 33b07 protein

MNGVEGNNELPLANTSTLSALVPEDLDLKQDQPLSEETDTVREMEAAGEAGAEGGASPDSEHCDPQLCLRVAENGCAAAAG
EGLEDGLSSSKCGDAPLASVAANDSNKNGCQLAGPLSPAKPKTLEASGAVGLGSQMMPGPKTKVMTTKGAISATTGKEG
EAGAAMQEKKGQVQKEKKAAGGGKDETRPRAPKINNCMDSLEAIDQELSNVNAQADRAFLQLERKFGMRRLHMQRFSFI
QNIPGFVWTAFRNHPQLSPMISGQDEDMRYMINLEVEELKHPRAGCKFKFIFQSNPYFRNEGLVKEYERRSSGRVVSLS
TPIRWHRGQEPQAHIHNRNREGNTIPSFFNWFSDHSLLEFDRIAETIKGELWSNPLQYYLMGDGPRRGVRVPPRPVESPR
SFRFQSG.

Rat 33b07 DNA (coding: 85-1308)

GGTGGAGCTAAGCACTCACTGCGGTGCTGCCCTGCGTCTGCAGAGAACAAGGAAAGCTTCTCTGCAGGGCTGTCAGCTGC
CAAAATGAACGGCGTGGAAGGGAACAACGAGCTCCCTCTCGCTAACACCTCGACCTCCGCCCTTGTCGGAAGATCTGG
ATCTGAAGCAAGACCAGCCGCTCAGCGAGGAACTGACACGGTGCGGGAGATGGAGGCTGCAGGTGAGGCCGGTGCGGAG
GGAGGCGCGTCCCCCGATTGCGAGCACTGCGACCCCCAGCTCTGCCTCCGAGTGGCTGAGAATGGCTGTGCTGCCGAGC
GGGAGAGGGGCTGGAGGATGGTCTGTCTTCATCAAAGTGTGGGGACGCACCCTTGGCGTCTGTGGCAGCCAACGACAGCA
ATAAAAAATGGCTGTGAGCTTGCAGGGCCGCTCAGCCCTGCTAAGCCAAAACTCTGGAAGCCAGTGGTGCAGTGGGCCTG
GGGTGCGCAGATGATGCCAGGGCCGPAAGAAGACCAAGGTAATGACTACCAAGGGCGCCATCTCTGCGACTACAGGCAAGA
AGGAGAAGCAGGGGCGGCAATGCAGGAAAAGAAGGGGTGCAGAAAGAAAAAAGGCAGCTGGAGGAGGGAAAGACGAGA
CTCGTCTTAGAGCCCCCTAAGATCAATAACTGCATGGACTCCCTGGAAGCCATCGATCAAGAGCTGTCAAATGTAAATGCG
CAAGCTGACAGGGCCTTCTCCAGCTGGAACGCAATTTGGGCGGATGAGAAGGCTCCACATGCAGCGCCGAAGTTTCAT
CATCCAAAACATCCCAGGTTTCTGGGTACAGCGTTTTCGGAACCACCCGCAACTGTACCGATGATCAGTGGCCAAGATG
AAGACATGATGAGGTACATGATCAATTTAGAGGTGGAGGAGCTTAAGCACCCCAAGAGCAGGGTGCAAATTTAAGTTCATC
TTCCAAAGCAACCCCTACTTCCGAAATGAGGGGCTGGTCAAAGAGTACGAGCGCAGATCCTCAGGTGAGTGGTGTGCGT
CTCTACGCCAATCCGCTGGCACCAGGGGTCAAGAACCCAGGCCCATATCCACAGGAATAGAGAGGGGAACACGATTCCCA
GTTTCTTCAATTGGTTCTCAGACCACAGCCTCCTAGAATTCGACAGAATAGCTGAAATTATCAAAGGGGAGCTTTGGTCC
AATCCCTTACAATACTACCTGATGGGCGATGGGCCACGCAGAGGAGTTTCGAGTCCACCAAGGCAGCCAGTGGAGAGTCC
CAGGTCTTTCAGGTTCCAGTCTGGCTAAGCTCTGCCCTCGTGAGAAGCTCTTACAGAAGAGTCCTTACCACCTTCTCAGC
TTGGCTAGCAGCATGCAGCCTTCTGTCTGCTTTCTCTTCCCTTGGAATTGTGTCTTTTGGTTCTTCTAAGTCTCCGGTAGTT
TCAAGGTTGTGGCTTCAAAGTCTTTGCTCTTCTTTCTCTTGGCCATCACGATGTCCTGCATAGTGTAAAGGTGTTCCAA
GTGCATGGCCTCCAACTGCTTCTATGCCAAGCTCACGTGCTGTAGTTTGTACTGCTTTTCTTTGCATGGCTTGGTTCTT
GTCTGTGATCTTCTAGGTTTTTTGTTTTCTTTTTTAAAGTGGTTCTCTATCAAAGAAAGCTTGACATATCCTTACCAA
GAACTAGCCAGATTTTACTACTGTGTTCCCGATATCTATGTACTGTGAAGAACTGTGAGTTTCGCCACTGCAAGATGGGAC
TGTATCCCAATCCAGCCATCAGCCCAACAGGACATTCCAAGCTGTACCAACTGATCCTAGCTGTCTTCTGGGCCCTTTG
CCATTTACCCTGCTTTTTTATCTATAGAATGAGCAGGTGGCTGGTAGGTGACTACTAGGTAAGAGTGAAGTATTAGGTGAG
GAGTGTCTTCTGTACCCACATTGTTCTTGTACCAATGCATCATGATCAGCTTGGATCAGCTACTGACTGTCTGATATTTT
TAACCCCCAACACAAAAA

Fig. 26

32/48

Human 33b7 (106d5) DNA (coding: 88-1332)

GGGGTGGTGTAGACGTTTCGGGcAGAGCTCGGCCGCTGCGGAGGACAAGGAACTCTCCCTCTCCACCTAGTCTGACTTC
TTCCAAAATGAGCGGCTGGATGGGGGCAACAAGCTCCCTCTCGCCCAAACCGGCGGCCTGGCTGCTCCCGACCATGCGCT
CAGGAGATCCGGACCTAGACCAGTGCCAAGGGCTCCGTGAAGAAACCGAGGCGACACAGGTGATGGCGAACACAGGTGGG
GGCAGCCTGGAGACCGTTGCGGAGGGGGGTGCATCCCAGGATCCTGTGACTGTGGCCCCGCGCTCCGCGTCCCAGTTGC
CGGGAGTTCGCGCGGTGCAGCGACCAAGCCGGGAGGAGGATGCTCCACCTTCTACGAAAGGTCTGGAAGCAGCCTCTG
CCGCCGAGGCTGCTGACAGCAGCCAGAAAAATGGCTGTCAGCTTGGAGAGCCCCGTGGCCCTGCTGGGCAGAAGGCTCTA
GAAGCCTGTGGCGCAGGGGGCTTGGGGTCTCAGATGATACCGGGGAAGAAGGCCAAGGAAGTGACGACTAAAAACGCGC
CATCTCGGCAGCAGTGGAAAAAGGAGGAGAGACACGGCCAGGGCCCCGAAGATCAATAACTGCATGGACTCACTGGAGCCATCGAT
CAAGAGTTGTCAAACGTAAATGCCCAGGCTGACAGGGCTTCCTTCAGCTTGAGCGCAAGTTTGGCCGCATGCGAAGGCT
CCACATGCAGCGCAGAAGTTTCATTATCCAGAATATCCAGGTTTCTGGGTTACTGCTTTTCAAACACCCCCAGCTGT
CACCTATGATCAGTGGCCAAGATGAAGACATGCTGAGGTACATGATCAATTTGGAGGTGGAGGAGCTTAAACACCCCCAGA
GCAGGCTGCAAAATCAAGTTCATCTTTCAGGGCAACCCCTACTTCCGAAATGAGGGGCTTGTCAAGGAATATGAACGCAG
ATCCTCTGGCCGGTGGTGTCTCTTCCACTCCAATCCGCTGGCACCAGGCCAAGACCCCCAGGCTCATATCCACAGAA
ACCGGGAAGGGAACACTATCCCTAGTTTCTTCAACTGGTTTTCAGACCACAGCCTTCTAGAATTCGACAGAATTGCAGAG
ATTATCAAAGGAGAACTGTGGCCCAATCCCCTACAATACTACCTGATGGGTGAAGGGCCCCGTAGAGGAATTCGAGGCCC
ACCAAGGCAGCCAGTGGAGAGCGCCAGATCCTTCAGGTTCCAGTCTGGCTAATCTCTGTCTGTGAGAAGCTTCTGCACA
AGTTTCTTACCACTCCTCTTGGACCTAGCTTTCAGGCTTGGCCCAACAGATGCAGTCTTCCATCTGCTTTCTCTCATACTGTGG
ATTATCTTTTCTTGGTTCTAAATCTTCAGTAATCGGTTGCAAGATGTTGGCTTACCTGCCTGTGCCATTCTTCTCT
GGGCTTTCATGCTTTTCTGCATTGTGTTAACATGTTTCAAGTGCATGGCCTTCTACGGCTTCTATGCGATGCTATGATA
CTATAGATATAGTGTACCATCTGCTTTCTTTCATGCTTGGACCTATCTGTGACCATGCTCTTCTCCCAATTTAAG
TGGTCTGTACCAAGAAATCTTGATACATTTTCAAAATAACTGATTGGGCTTCTATCTTTATGCTGGCTGTGTCTCTG
ATACCATGTACTTATGGTAAGCTATTTGGGTATTACCACTGCAAGACAAAACCTGATATCTTAACCCGGCCATCAACCCA
AATTGGACATTCAGACTACCACCAACTGGATCCAGCTGCCTTCTGGGCTTGTGCCATCCACCCTACTGGTTATCTGA
TAGAACAAAGCTGGTGGCTGATGGGTGACTGCTAGGCGTGACTGAGGTAAATAGATGAAAAGTGTTCTATGTTATCACATTG
GTTTTCTGTACTTTTGGTTACTCTACGTCTACGCTACGACCCAGCTGCTGGTGATGATGAAGCCTGTGCTATAGCCCACCCCTACT
CACTCTCACCTTCTGGTTGAACCTTGTCTAGGCCACCATTGTCTGCCTCATCAGGAACCTATCTGTAGACGATGCTCCAG
GGAGCTCACAGCAACACCCCTTACCACCAGGATGGGCGAGTAATATGTGACAGAGCCCAAGCAAGGCTGGAACGCAGTCC
CTCCAGCTTAGTCTTTCTGACTCCTAGCCAACAAACCATCCTTAATGTGAGCAACTTCTTTAGGCATTTCTCTTTTCC
CCGCTGCACCCACTCTGAACATGACAAAAGTTGCCAGAGTTGGGGCATTGAGGAAGAGATATTTCTGGAATGTGAGACT
TGTTATGCCTCTGTCTCTTCTCTCCCTCCCCCTCCCCCTCTCCCTCCCCCTCTCCCTCCCATCCCTTTTCTTCCCTTTCA
CTCTGAAGCAGTTTATGCTTTATTAACAGAAAACAAAACCTGGCAAAGCAGGCTTTTGTGTTAATTTGCTCTTTCCCTGATT
GTGTTTCAGAGAGAAAGGTTATGATTAAATGGGCTCCAGATCTCTTATTGCCCTTATCTCCACCCACTTCTTTTAGCA
TTTATCTTTTACCCCATCCATTCTACCAAAACCTGTGTATTTCTTGAGTTTGTGTTGAGAAGCTGGAAGAGAGAGAGA
AGGGCCTCACAGTGATGGGTTCAGGACGGGTCAAAGGCAAAGGCCTTTGTGATGTGAGCAAAGGCAACCAAACTTAGCC
TCACTCCACTTTTCTAAAGATGGAATTTCTTTTTTGGGCTTGGAGTCTTCTAGGGTAGCATTGTGAGGTCACTCTTC
TCCTTTGTACTATTTGTTTCTGCCCTGATGTCCCTTGGGTCTCCATCCTACTGCCTGGCTTTCTTGGCCCTCATTCTCTC
AGCTTCTGCATTTCCCTGCCCTGCTCCTAACAAATGAAGAAGCAGGCTGCAGCCTGCATTGTGGAAGATCTCCAGCCTCCT
TGTAGGGGATATCCGGGATGTGTAGCATCTGTGTGATTTCACGGACAAGTTCCAGTAGGTGGGACAGTGATGCCGTCAA
GGCTTAGTTATGATCATGTGTGGTGATAAAGACCATCCACCTACCCCTTTTCCCTTTTGAAGGCTTGGCCCTA
AGCTACCTGAGGGTTTAGGAGGTCTGAACACACACAGTGGAGAGGTTAATCTAGGTTGGGAAACTGAGTAAAGTCCAGA
GCAGGAATGAGCCTGCTGTGGCGTGGGTTTGGAAAGGCTCACAGGAAGAACCTGCAGGATCAGGGGTGGGAGGGGAGGC
CCCTGAGGTGCTCTCCAGGGAAGAGGGGCTGGGGTTTAAATAGCATGCTTGGAGGAAGATTTTCTTCAATTTTCTCTAA
GTCCTTGAATTCACAGTAGATTTTGTAAACAAAATGTAAGTCGATGTTTCTCTCAATTATCTTAGGAGTGACCTTTA
TATGTGTGGAAGATTAATGGTATATGCTCCTTATGTCACTGTTTTTGTGATAAAATCCATTTCTTTCTGTCTTACGCT
ATGACAAAATTTGATGTTTACAGGCTGCTTTTGTCTTATAATTGACAACATGTGCAAAAATACCAATTTGTGTCTGTG
CAGTATGAAGAATTCAGTGAATATTATTAATGATATTAGCTTGTGTTTTGCTCTCTGTTTATATGAGCTTATCTTAGAA
ATATAATTTGAATGTGATCTTTCAATAGTCTGAATATTTTACAAATATAGCTATGTCTTGTGAAATGAGCTTAAAG
AAAAATACGACTCTGTGTCTTACTTGATATTTCTTGGCCTAGTAATGTACTTGACATTTATGTTCTTAAGCAGTGTAAAG
TACCAGTAGAATTTCTGTCAAACCTCAATGATCATTTAGTACTTTTGTCTTCTCCCATGTGCTTGAAGGAAAAATAAAG
TGTCACTACCGTATTTCTTGTGTTTTCATCAAAAAATAAAATAATTTAAAAAACAAAAA

Human 33b7 (106d5) protein

MSGLDGGNKLPLAQTGGLAAPDHASGDPDLQDQGLRETEATQVMANTGGGSLETVAEGGASQDPVDCGPALRVPVAGS
RGGAATKAGQEDAPPSTKGLEAASAAEAADSSQKNGCQLGEPRGPAGQKALEACGAGGLGSQMIPGKKAKEVTTKKRAIS
AAVEKEGEAGAAMEEKVVQKEKKVAGGVKEETRPRAPKINNCDLSLEAIDQELSNVNAQADRAFLQLERKFGMRRLHM
QRRSFIIQNIPIGFVWTAFRNHPQLSPMISGQDEDMRLYMINLEVEELKHPRAGCKFKFIFQGNPYFRNEGLVKEYERRSS
GRVVSLSPIRWHRGQDPQAHIRNREGNTIPSFNWFSDHSLLEFDRIAEIIKGLWPNPLQYYLMGEGPRRGIRGPPR
QPVESARSFRFQSG

Fig. 27

SUBSTITUTE SHEET (RULE 26)

33/48

Rat 1p protein (partial)

LKGARPRVNVNSTCSDFNHGSALHIAASNLCLGAARKLLEHGANPALNRKQVPAEVVPDPMDSLDKAEALVAKELRT
LLEEAVPLSCTLPKVTLPNYDNVPGNMLLSALGLRLGDRVLLDGQKTGTLRFCTTEFASGQWVGVELDEPEGKNDGSVG
GVRIFYICPPKQGLFASVSKVSKAVDAPPSSVTSTPRTPRMDFSRVTGKGRREHKGKKKSPSSPSLGLSLQREGAKAEVGD
QVLVAGQNRDCAFLWEDRLCSRLLVWH

Rat 1p DNA (partial, coding:1-804)

CTGAAAGGGGCGAGGCCAGGGTGGTGAACCTCCACCTGCAGTGACTTCAACCATGGCTCAGCTCTGCACATCGCTGCCTC
GAATCTGTGCCTGGGCGCCGCCAAATGTTTACTGGAGCATGGTGCCAACCCAGCGCTGAGGAATCGAAAAGGACAGGTAC
CAGCGGAAGTGGTCCCAGACCCCATGGACATGTCCCTTGACAAGGCAGAGGCAGCCCTGGTGGCCAAGGAATTGCGGACG
CTGCTAGAAGAGGCTGTGCCACTGTCTGCACCTTCTCTAAAGTCACTACCCAACTATGACAACGTCCCAGGCAATCT
CATGCTCAGCGCGCTGGGCTGCGTCTAGGAGACCGAGTGCTCCTCGATGGCCAGAAGACGGGCACGCTGAGGTTCTGCG
GGACCACCGAGTTCGCCAGTGGCCAGTGGGTGGGCGTGAGCTAGATGAACCGGAAGGCAAGAACGACGGCAGCGTTGGG
GGTGTCCGGTACTTCATCTGCCCTCCCAAGCAGGGTCTCTTTGCATCTGTGTCCAAGGTCTCCAAGGCAGTGGATGCACC
CCCCCATCTGTACCTCCACGCCCCGCACTCCCCGGATGGACTTCTCCCGTGTAACGGGCAAAGGCCGGAGGGAACACA
AAGGGAAGAAGAAGTCCCCATCTTCCCCATCTCTGGGCAGCCTGCAGCAGCGTGAAGGGGCCAAAGCTGAAGTTGGAGAC
CAAGTCCTTGTGGCAGGCCAGAACAGGGATTGTGCGTTTCTATGGGAAGACAGACTTTGCTCCAGGTTACTGGTATGGCA
TTGAACTGGACCAGCCACGGGCAAGCATGACGGCTCTGTGTTCCGGTGTCCGGTACTTTACCTGTGCCCCGAGGCACGGG
GTCTTTGCACCAGCATCTCGTATCCAGAGGATTGGTGGATCCACTGATCCCCCTGGAGACAGTGTGGAGCAAAAAAAGT
GCATCAAGTGACAATGACACAGCCCAAACGCACCTTCACAACAGTCCGGACCCCAAAGGACATTGCATCAGAGAACTCTA
TCTCCAGGTTACTCTTCTGCTGCTGGTTTCTTGGATGCTGAGGGCGGAGATGCAGTCTTAGAGACCTGGATACCTGACA
CAGAGACAGAGTCCCTCTAGCATCTCTGACACAAGGAGACCCCAAGTCACCCCTAAGATAGAGATTCCCAGTGACACCTC
CAGAATAGAAAACCCGTTAGCCAGCCCTCGATTACTGAGGTCCCATTTAATACAGATCTCCCATGACGACTCCCCCAAAT
ACAGACCTCATGTTACCCCAAAGAGATTCCCTGAGTAGCACCTTCAGGCTAGTCCCTGTCCCTTACCCCTCAGAGCAGA
TTTCCCCCAATAAACATTTTCCACATCACCCAAGGGATGCTGACCCTCTCCACGACAGGACGTTCTTGGAGTTACCAGTGG
ATTAGAGTCCCATGAATGAAGACCCCCCCCCACCCCGGTTCTCTTAAGCATAGGTCATACCTCCAGAATAGCCAGCCACA
TCACTATCCCCATGTAACATCAGTCTCCTCAAAATGGCGTGAGGTCACTAGAAAGACCTTATACTCTCCTCTCCTTCTCA
GAGATGCCCTCCATTCACTTAAGTCCCTGTTCTCACCCCTGAACAAGACACCTAATTAACCGGCCCCACTCACCTCAATTA
CAAACACCAAAATCGTCTGGAAGCATGAATTACAGGACAGCAAGTCTTCCCTGCCCTCTGCACCCCTTGAGAAAACCCCAAG
TGCCTTGTATGAAGCCCAACCCACATGGCCACAGTCCCTGTGCTGGCCAAGGCTCCCAGAAAATTCTCTATTTTTTAA
GTAATAACTTCCCCCCTTTGGGGGGATCCCCAAATTTGGAGACCCCATTTCTAGAACACTGGGGAGTTCAAATTCAGAG
AGAATATATATATATATAATCCCCAATTCCTCATGCTTCCAAGCCCTACAATCTCTAGAAGACCCCAAATTTCTAATTC
CCAGGACTTCCCTTACCAAGTCACAGAATCTTCAAATCCCCAGGGAATCCCCAACTTAAGATACCAATCCCCAACCCCTC
AGGAAATCCCCCAACACAAGGTCCTTAGGACCGGGAGGAAGGAACCTGTTGCCAGGAGAACATCCCAGGCTCTCAGGGCA
TCTCAAACCTGACTCCCAGGCACCAGGAGACCCCAAACAGAAAAGTCCCATCTTTGGAACAAGGATAGGACTCTAATACCC
TTAGTCCATGGATCTTTAATTTCCCAACCTCCAACTCCATGGGCCCCCACCCTCAAGGGAACCCCAAGATCCAAATCTC
TGATAACTAATATGTGCAGGGCCCCAGGGCTCTAACAGGACCCCAAATCATGGAGTCCCTACTTCAATCTACCTTCTGGT
CACAGGTCCAAGACACTAAATCTGAGTCATTGGCCCCAAAGGACTTCACAGCACCTGGGCCAGACTAACAGCCTGAGGGA
GAACCTGAGGGCCCCGTGGGTCCAGAGCAGACCTGGGGCCCTGACCACCAAGGACAGCTCAGACTGCCCTTCACTGCA
TGTCCCTAAACTCAGCATGACTCCTGTCTCTTCAATAAAGACGTTTCTATGGCAAAAAAAAAAAAAAAAAAAAAAAA
AAA

Fig. 28

34/48

Rat 7s Protein (partial)

ADSTSRWAEALREISGRLEAMPADSGYPAYLGARLASFYERAGRVKCLGNPEREGSVSIVGAVSPPGGDFSDPVTSATLG
IVQVFWGLDKKLAQRKHFPVSNWLISSKYMRLALDEYYDKHFTEFVPLRTKAKEILQEEEDLAEIVQLVGKASLAETDKI
TLEVAKLIKDDFLQONGYTPYDRFCPFYKTVGMLSNMISFYDMARRAVETTAQSDNKITWSIIREHMGEILYKLSSMKFK
DPVKDGEAKIKADYAQLLEDQMNAFRSLED

Rat 7s DNA (partial, coding: 1-813)

GCTGACTCTACCTCTAGATGGGCTGAGGCCCTCAGAGAAATCTCTGGTCGCTTAGCTGAAATGCCTGCAGATAGTGGATA
CCCTGCATACCTTGGTGCCCGACTGGCTTCTTTCTATGAGCGAGCAGGCAGAGTGAAATGTCTTGAAACCCCTGAGAGAG
AAGGGAGTGTGAGCATTGTAGGAGCAGTTTCTCCACCTGGTGGTGATTTTTCTGATCCAGTCACATCTGCTACTCTGGGT
ATTGTTTCAGGTGTTCTGGGGCTTGATAAGAAGCTAGCTCAGCGCAAGCACTTCCCGTCCGTCAACTGGCTCATTAGCTA
CAGCAAGTACATGCGCGCCCTGGACGAGTACTATGACAAACACTTCACAGAGTTCGTGCCTCTGGAGACCAAAGCTAAGG
AGATTCTGCAGGAAGAGGAGGATCTGGCGGAAATCGTGCAGCTCGTGGGAAAGGCGTCTTTAGCAGAGACAGATAAAATC
ACCTTGGAGGTAGCAAAAACCTTATCAAAGATGACTTCCTACAACAAAATGGGTACACTCCTTATGACAGGTTCTGTCCATT
CTATAAGACGGTGGGGATGCTGTCCAACATGATTTTCATTCTATGATATGGCCCGCCGGGCTGTGGAGACCACCGCCCGAGA
GTGACAATAAGATCACATGGTCCATTATCCGTGAGCACATGGGGGAGATTCTCTATAAACTTTCCTCCATGAAATTCAAG
GATCCAGTGAAGGATGGCGAGGCAAAGATCAAGGCCGACTACGCACAGCTTCTTGAAGATATGCAGAACGCATTCCGTAG
CCTGGAAGATTAGAAGTGTGACTTCTCTCCTCCTCTCCGCAGCTCATATGTGTATATTTTCTGAAATTTCTCATCTCCA
ACCTTTTGCTTCCATATTGTGACGCTTTGAGACTAGTGCCTCGTGCCTTCTCGTTCATTTTGCTGTTTCTTTGGTAGGTC
TTATAAAACACACATTCTGTGCTCCGCTGTCTGAAGGAGCTCCTGACCTTTGTCTGAAGTGGTGAATGTAGTGCATATG
ATACACAGTGTAAACATACACATTGTAACATATACGTTCTGTAACTTGTATGTAAGGTGACTACCCCTTCCCTCCTCTCC
AGTAACTGTAAACAGGACTACTGCATGTGCTCTATTGGGGATGGAAGGCCAGATCTCCATACCGTGGACAGGTACATAA
GGAACTAGACCACTTGCAACTTAGTGTTTGTGTAGTAACCAATTTTGAGGAAGTATTTCCATTTAAAAACAAAAGATT
AATGTTCCAATTATTTGTAGCTTCCCCAGTATCAATCAGGACTGTTTGTGGCGCACTGGGAACATTTTTGTTTTCTTAA
CAGACGTTTGCAAGGCTGAACGTAATAGATAAATCAGTTCCTCTGAAAGTGTGAAAGTAAAAAGAGAGCTAGGTGGTCA
GACTTAAATTGACATCGTCTTGTTTAAGCATATTTTATTTCACTGAGAGATTTAATATCAAGGACTTTTATATACTCAAT
TACTAGGAAATCTTTTTTAAAGTACAATTTAAAAATCATTGAAATGTGATCCACATCATAGCCATTTTCTTATATTTA
GTCAGATGAGCTCAGAGTGGGGAGGGTGTGGGTTAGAATACCACAAGGACACGCAGCAGTGCCTGCAGGCAGTGTGGCCG
GGGGCCAGAGCGGCATTGTTTTACGAGGTACGTGTGTGGCGTGTGTGTTTGTCTTGTGACACTCTGAAAACAGCAAGCT
TACCAGTTCAGGAAATATTTTGTCTTTCTTCACTGGCTCAGAAAGCTCCTCAAAGTACCTGGTCCCTGAAGCTTCCTAT
CTGTTAATAGAGACGAGAGAGGTTCTTAAATTTAACTGGTGACAAAACAAAAGAAAAAAGATCGATTTTGTCTTGC
TGTTTTGGTGTGTTTAAATAATAATTCCATATTTGCATAACGAGGCTCGCTTCTGAGAGCTTGGAGATCGTGCTCCCTCT
TCACTCTCCGGGGTGATAATGCTGGCGCCATGCTACCTCTTCAGGAGGGGAAGGGGATTGAACATGGCTAACACTCTCAA
GTACACAAGCGTAACGACAAAGTATTTATTTTAAAGCCTTGGTATGTTGTTTAAATTATTAGGTGGTGCATTTCTTATGGT
CTTTTGGGTAGACATAGTATACACTTCAGATGTAATGTGTAAATCCTTGCTAGTGCATGTCTACACGATAGACTGCTATT
CAAGAAGGATATTCTTCCACATAACAATTTAAAACTATTAAATCAGATATGGATTATGCAATGACTTGTGAGAGGTGG
ATTAACGGTGTCTGCTTAATCAGTTTGTCTTCCAATATGGCTTCGTATCCAGAAGCCCTGACTAGTGGAGATGAGAAAGATT
TCAAAACCTGTCTGCCTACACCTACCAGCAACCTAGGCTTGTGATCAGAATGAATGATCCCAAGAACTACTTGACCAAG
TGTGTTTTGTTGTCTTGGATTTGAGATGTGCGTTCTTCTCCCTCTGAGACTGTTGATGTATGAGTGTGAAGAAGTTACA
GAAACAACGCTCAGATTTTACGGTAACCTTCCCTCTGCCACACTGTAGAGTTTCAGATTGTTCACTGATAGTGCTTCT
TTCGTAAGGATGTGTTAAATATAGCAGTCTTTTTTAAAGATTATGCAGTTCTCTATTTATTGTGCTGTGCCTGGTCTTA
AGTGCAGCCGGTTAAACAAGTTTTCATATGTATTTTTCCAGTGTTAAATCTCATACCTATGCCCTTGGAAAGCTCCATCC
TGAACAATGAATAGAAGAGGCTATATAAATTGCCTCCTTATCCTTAAGATTTCACTATCTTTATGTTAAGAGTAATGTAT
AATTATTAAATCTATGAAAAATAAAAAGTGGATTTAAATTAAGAGATC

Fig. 29

35/48

Rat 29x protein

ARLPAPPEHARQQPLLSGPEPGSSARVPVPGVASRRQPRGGKPPSGDGLSEGPSRPLLHARGEAGLHRQSGRVPHTGTAY
FADEPTEAQAPGGFCVSPSLLGVRWPACATRTPGSLPLSPPSAQPRTLWPTPPAGPSSRMVARNQVAADNAISPASEPRR
RPEPSSSSSSSSPAAPARPRPCPVVPAPAPGDTHFRTRSHSDYRRITRTSALLDACGFYWGPLSVHGAHERLRAEPVGT
FLVRDSRQRNCFALSVKMASGPTSIRVHFQAGRFLDGSRETFDCLFELLEHYVAAPRRMLGAPLRQRRVRPLQELCRQ
RIVA AVGREN LARIPLNPVLRDYLSSFPFQI

Rat 29x DNA (coding: 433-1071)

GCACGGCTCCCGGCCCCGGAGCATGCGCGACAGCAGCCCCCTCCTCtCCGGCCCTGAGCCCGGATCGTCCGCCCCGGTTCC
AGTTCCCGGCGTGCCAGTAGGCGGCAGCCGCGAGGCGGCAAGCCACCCAGCGGGGACGGCCTGGAGTCGGGCCCCCTCTC
CACGCCCCCTTCTCCACGCGCGCGGGGAGGCAGGGCTCCACCGCCAGTCTGGAAGGGTTCCACATACAGGAACGGCCTAC
TTCGCAGATGAGCCACCGAGGCTCAGGCTCCGGGCGGATTCTGCGTGTACCCCTCGCTCCTTGGGGTCCGCTGGCCGGC
CTGTGCCACCCGGACGCCCCGGCTCACTGCCTCTGTCTCCCCATCAGCGCAGCCCCGGACGCTATGGCCACCCCTCCAG
CTGGCCCCCTCGAGTAGGATGGTAGCACGTAACCAGGTGGCAGCCGACAATGCGATCTCCCCGGCATCAGAGCCCCGACGG
CGGCCAGAGCCATCCTCGTCCTCGTCTTCGTCTCGCCGGCGGCCCCGGCGCGTCCCCGGCCCTGCCCGGTGGTCCCCGGC
CCCGGCTCCGGGCGACACTCACTTCCGCACCTTCCGCTCCCACTCTGATTACCGGCGCATCACGCGGACCAGCGCTCTCC
TGGACGCCTGCGGCTTCTACTGGGGACCCCTGAGCGTGCATGGGGCGCACGAACGGCTGCGTGCCGAGCCCGTGGGCACC
TTCTTGGTGCGCGACAGTCGCCAGCGGAAGTGTCTTTCGCGCTCAGCGTGAAGATGGCTTCGGGCCCCACGAGCATTCG
TGTGCACTTCCAGGCCGGCCGCTTCCACCTGGACGGCAGCCGCGAGACCTTCGACTGCCTCTTCGAGCTGCTGGAGCACT
ACGTGGCGGGCGCCGCGCCGCATGTTGGGGGCCCCACTGCGCCAGCGCCGCGTGCGGCCGCTGCAGGAGCTGTGTGCCAG
CGCATCGTGGCCGCGCTGGGTGCGGAGAACCCTGGCAGCATCCCTCTTAACCCGGTACTCCGTGACTACCTGAGTTCCTT
CCCCCTCCAGATCTGACCGGCTGCCGCGCTGCCCGCAGCATTAAGTGGGAGCGCCTTATTATTTCTTATTATTAATTATT
ATTATTTTTTcTGAACACAGTGGGAGCCCTCCCCGCTAGGTGCGAGGGAGTGGGTGTGGAGGGTGAATGCCTCCCACT
TCTGGCTGGAGACCTTATCCCGCTCTCGGGGGGCTCCCCCTCGGTGCTCCCTCCCGGTCCCCCTGGTTGTAGCAGCT
TGTGTCTGGGGCCAGGACCTGAACCTCACGCCTACCTCTCCATGTTTACATGTTCCAGTATCTTTGCACAAACAGGGG
TGGGGGAGGGTCTCTGGCTTCATTTTTCTGCTGTGCAGAATATTCTATTTTTATATTTTTACATCCAGTTTAGATAATAAA
CTTTATTATGAAAGTTTTTTTTTTAAAGAAAAAAAAAAAAAAAAAAAAA

Fig. 30

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Rat 25r DNA (coding 130-

GGCACGGCTCCCGGCCCCGGAGCATGCGCGACAGCAGCCCCGGAACCCCCAGCCGCGGCGCCCCCGGTCCCGCCGCCAGC
GCAGCCCCGGACGCTATGGCCCCACCCCTCCAGCTGGCCCCCTCGAGTAGGATGGTAGCACGTAACCAGGTGGCAGCCGACA
ATGCGATCTCCCGGCATCAGAGCCCCGACGGCGGGCCAGAGCCATCCTCGTCCTCGTCTTCGTCTCGCCGGCGGGCCCCG
GCGCGTCCCGGCCCCGCCCCGGTGGTCCCGGCCCCGGCTCCGGGCGACACTCACTTCCGCACCTTCCGCTCCCACTCTGA
TTACCGGCGCATCACGCGGACCAGCGCTCTCCTGGACGCGCTGCGGCTTCTACTGGGGACCCCTGAGCGTGCATGGGGCGC
ACGAACGGCTGCGTGCCGAGCCCGTGGGCACCTTCTTGGTGCGCGACAGTCGCCAGCGGAAGTGTCTTTCGCGCTCAGC
GTGAAGATGGCTTCGGGCCCCACGAGCATTCTGTGCACTTCCAGGCCGGCCGCTTCCACCTGGACGGCAGCCGCGAGAC
CTTCGACTGCCTCTTCGAGCTGCTGGAGCACTACGTGGCGGGCGCCGCGCCGCATGTTGGGGGCCCCACTGCGCCAGCGCC
GCGTGCGGGCCGCTGCAGGAGCTGTGTCGCCAGCGCATCGTGGCCGCGCCGCGCCGCATGTTGGGGGCCCCACTGCGCCAGCGCC
AACCCGGTACTCCGTGACTACCTGAGTTCCTTCCCCCTTCCAGATCTGACCGGCTGCCGCCGTGCCCGCAGCATTAAAGTGG
GAGCGCCTTATTATTTCTTATTATTAATTATTATTATTTTCTGGAACCACGTGGGAGCCCTCCCCGCCTAGGTCCGAGG
GAGTGGGTGTGGAGGGTGAGATGCCTCCCACTTCTGGCTGGAGACCTTATCCCGCCTCTCGGGGGGCTCCCCCTCCTGGT
GCTCCCTCCCGGTCCCCCTGGTTGTAGCAGCTTGTGTCTGGGGCCAGGACCTGAACCTCCACGCCTACCTCTCCATGTTTA
CATGTTCCCACTATCTTTGCACAAACCAGGGGTGGGGGAGGGTCTCTGGCTTCATTTTTCTGCTGTGCAGAATATTCTAT
TTTATATTTTTTACATCCAGTTTAGATAATAAACTTTATTATGAAAGTTTTTTTTTAAAAAAAAAAAAAAAAAAAAA

Fig. 31

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Rat 5p protein

MPSQMEHAMETMMLTFHRFAGEKNYLTKEDLRVLMEREFPGFLENQKDPLAVDKIMKDLDQCRDGKVGFSFLSLVAGLI
IACNDYFVVHMKQKK

Rat 5p DNA (coding: 52-339)

CTTCCAAAGACTGCAGCGCCTCAGGGCCCAGGTTTCAACAGATTCTTCAAAATGCCATCCCAAATGGAGCATGCCATGGA
AACCATGATGCTTACATTTACAGGTTTGCAGGGGAAAAAACTACTTGACAAAGGAGGACCTGAGAGTGCTCATGGAAA
GGGAGTTCCCTGGGTTTTTGGAAAATCAAAAGGACCCCTCTGGCTGTGGACAAAATAATGAAAGACCTGGACCAGTGCCGA
GATGGAAAAGTGGGCTTCCAGAGCTTCTATCACTAGTGGCGGGGCTCATCATTGCATGCAATGACTATTTTGTAGTACA
CATGAAGCAGAAGAAGTAGGCCAACTGGAGCCCTGGTACCCACACCTTGATGCGTCCTCTCCCATGGGGTCAACTGAGGA
ATCTGCCCCACTGCTTCCTGTGAGCAGATCAGGACCCCTTAGGAAATGTGCAAATAACATCCAACCTCCAATTCGACAAGCA
GAGAAAGAAAAGTTAATCCAATGACAGAGGAGCTTTCGAGTTTTATATTGTTTGCATCCGGTTGCCCTCAATAAAGAAAG
TCTTTTTTTTTTAAGTCCGAAAAAAAAAAAAAAAAAAAAA

Fig. 32

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Rat 7q protein

MAYAYLFKYIIIIGDTGVGKSCLLLQFTDKRFQPVHDLTIGVEFGARMITIDGKQIKLQIWDTAGQESFRSITRSYYRGAA
GALLVYDITRRDTFNHLTTWLEDARQHSNSNMVIMLIGNKSDLESRRVKKEEGEAFAREHGLIFMETSAKTASNVEEAF
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Rat 7q DNA (coding 1-639)

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Fig. 33

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Rat 19r protein

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Rat 19r DNA (coding 1-816)

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Fig. 34

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Monkey KChIP4c (jlkxa053c02) DNA sequence (CD: 122-811)

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Monkey KChIP4c protein sequence

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Fig. 35

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Monkey KChIP4d (jlkx015b10) DNA sequence (CD:64-816)

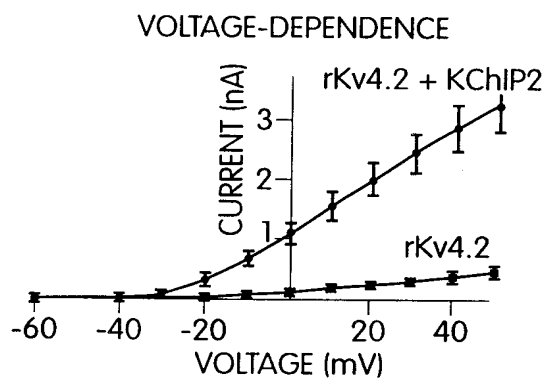
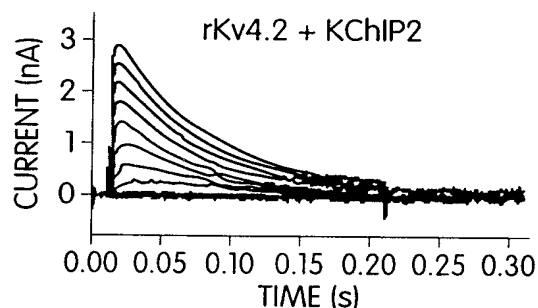
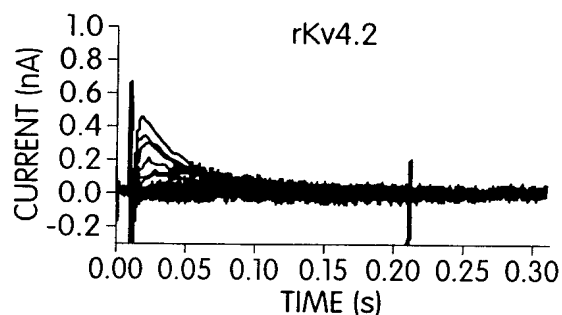
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Monkey KChIP4d protein sequence

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Fig. 36

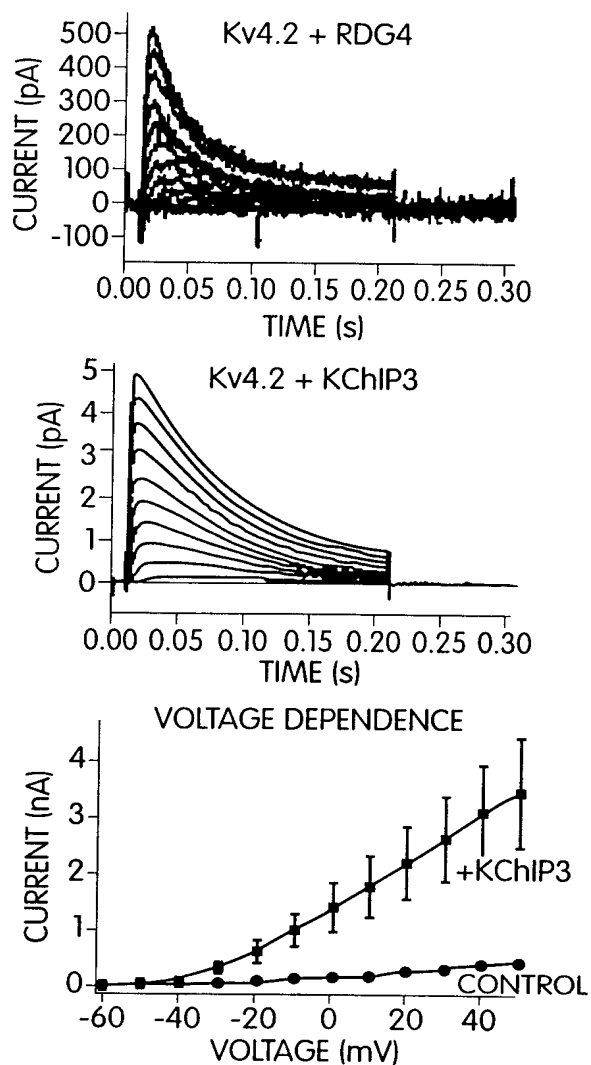
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CURRENT PARAMETER	CHO	
	rKv4.2	rKv4.2 + KChIP2
PEAK CURRENT (nA/cell, at 50 mV)	0.51 ±0.098	3.3 ±0.45
PEAK CURRENT DENSITY (pA/pF, at 50 mV)	18.6 ±2.8	196.6 ±26.6
INACTIVATION TIME CONSTANT (ms, at 50 mV)	28.47 ±3.5	95.14 ±8.3
RECOVERY FROM INACTIVATION TIME CONSTANT (ms, at -80 mV)	257.9	49.5
ACTIVATION $V_{1/2}$ (mV)	20.5	-2.2
STEADY-STATE INACTIVATION $V_{1/2}$ (mV)	-47.1	-45.7

Fig. 38

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CURRENT PARAMETER	CHO	
	rKv4.2 +RBG4	rKv4.2 +KChIP3
PEAK CURRENT (nA/cell, at 50 mV)	0.46 ±0.084	3.5 ±0.99
PEAK CURRENT DENSITY (pA/pF, at 50 mV)	29.7 ±11.2	161.7 ±21.8
INACTIVATION TIME CONSTANT (ms, at 50 mV)	29.5 ±9.5	67.2 ±14.1
RECOVERY FROM INACTIVATION TIME CONSTANT (ms, at -80 mV)	435.9	130.8
ACTIVATION $V_{1/2}$ (mV)	4.1	6.1

Fig. 39

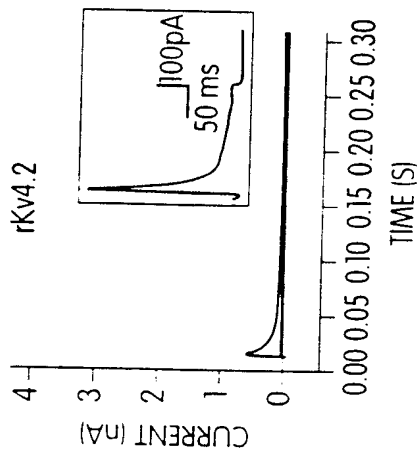


Fig. 40A

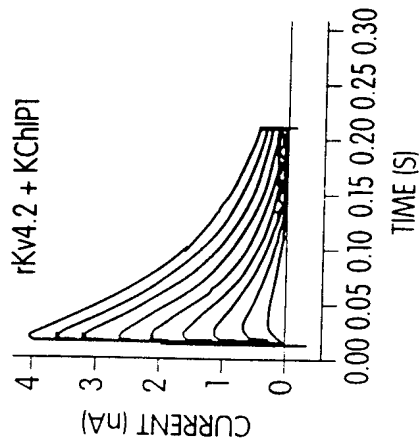


Fig. 40B

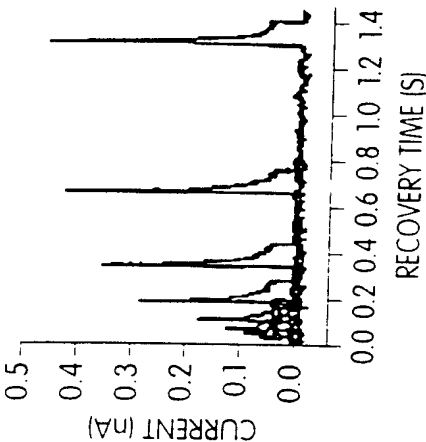
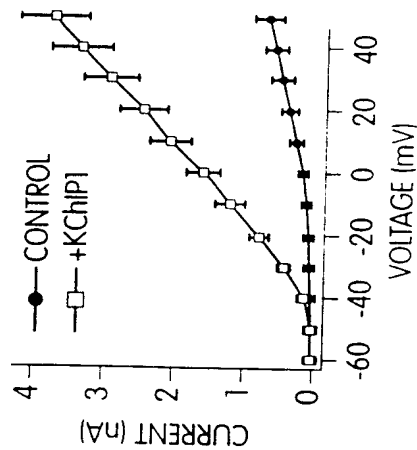


Fig. 40D

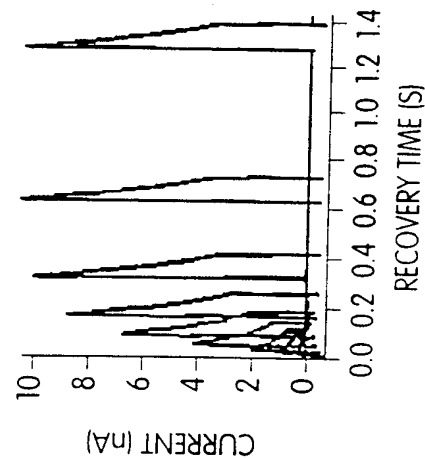


Fig. 40E

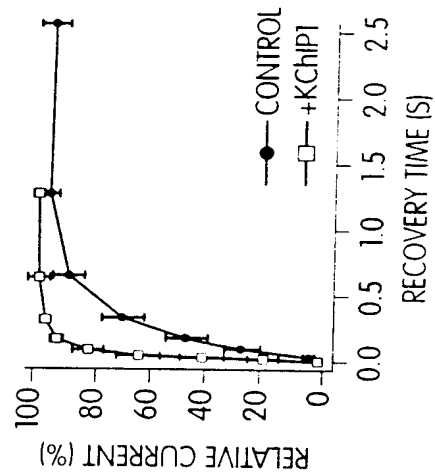


Fig. 40F

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 KChIP3 M - - - - - Q P A K E V - - - - - T K A S D G S L L G D L G H T P L S K K E G I K K W Q R P R L S R Q A L M R C C L V K W I L S S T - - - - -
 HIP M G K Q N S K - - - - -
 NCS1 M G K S N S K - - - - -

EF1
 X Y Z -Y -X -Z
 KChIP1 - - - - - D K I E D E L E M T M V C H R R P E G L E Q L E A Q T N F T K R R E L Q V L Y R G F K N E C P S G V V N E D T F K - - - - -
 KChIP2 P S V S E N S V D D E F F E L S T V C H R R P E G L E Q L E A Q T N F T K R R E L Q V L Y R G F K N E C P S G I V N E E N F K - - - - -
 KChIP3 A P Q G S D S S D S E L E L S T V R H H Q P E G L D Q L Q A Q T K F T K K E L Q S L Y R G F K N E C P T G L V D E D T F K - - - - -
 HIP - - - - - L R P E M L Q D L R E N T E F S E L E L Q E W Y K G F L K D C C P T G I L N V D E F K - - - - -
 NCS1 - - - - - L K P E V V E E L T R K T Y F T E K E V Q Q W Y K G F I K D C P S G Q L D A A G F Q - - - - -

EF2
 X Y Z -Y -X -Z
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 KChIP2 Q I Y S Q F F P Q G D S S N Y A T F L F N A F D T T N H D G S V S F E D F V A G L S V I L L R G T V D D R L N W A F N L Y D
 KChIP3 L I Y A Q F F P Q G D A T T Y A H F L F N A F D A D G N G A I H F E D F V V G L S I L L R G T V H E K L R W A F N L Y D
 HIP K I Y A N F F P Y G D A S K F A T F F V F N V F D D T N S D G T I D F R E F I A L S V T S F G R L E Q R L M W A F S M Y D
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EF3
 Y Z -Y -X -Z
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 KChIP3 L E A C Q K D D N I M S S M Q - - - - - L F E N V I .
 HIP I R G A K S D P S I V R L L Q C D P S S R S Q F .
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Fig. 41

NIKALI ET AL.

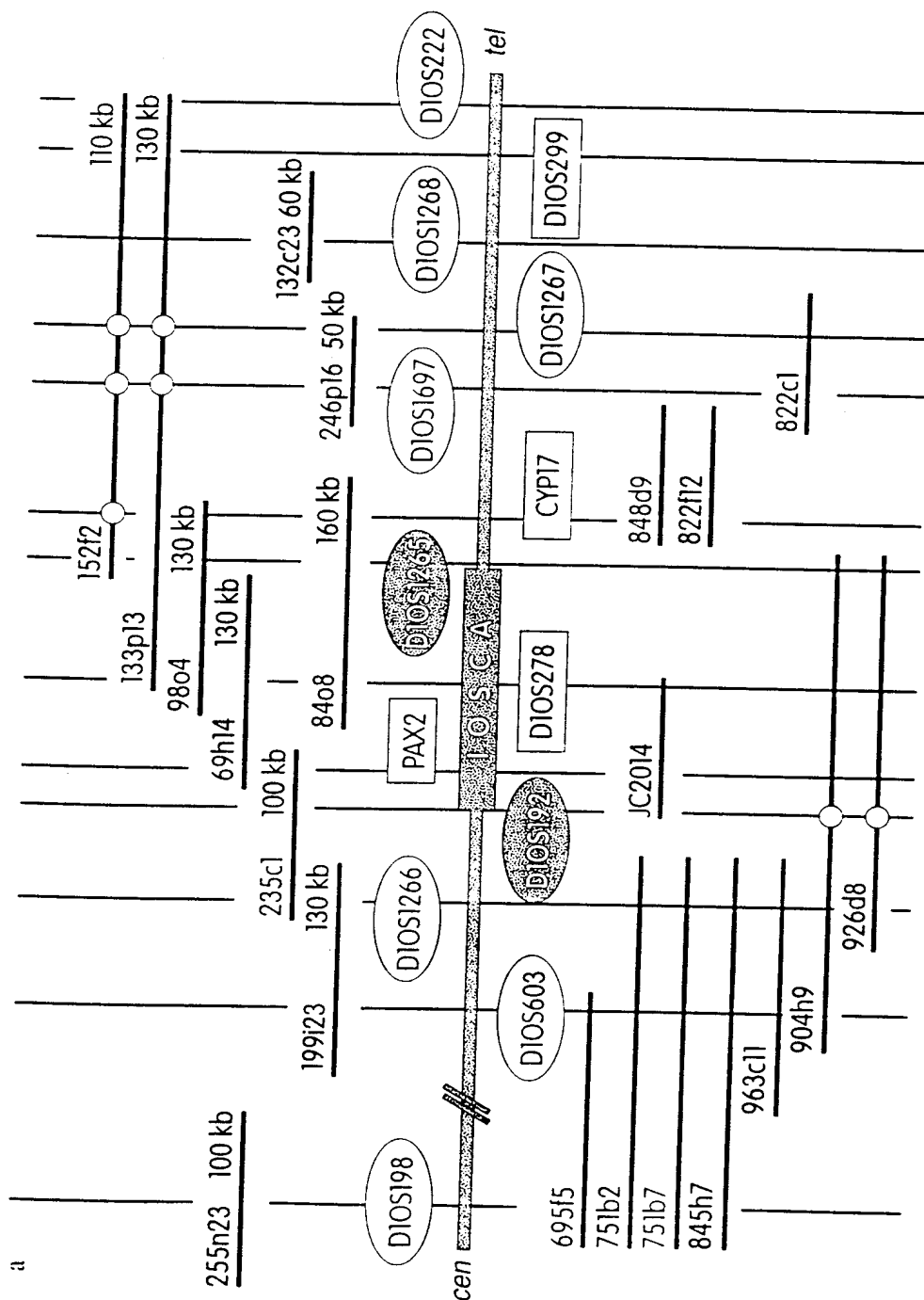


Fig. 42

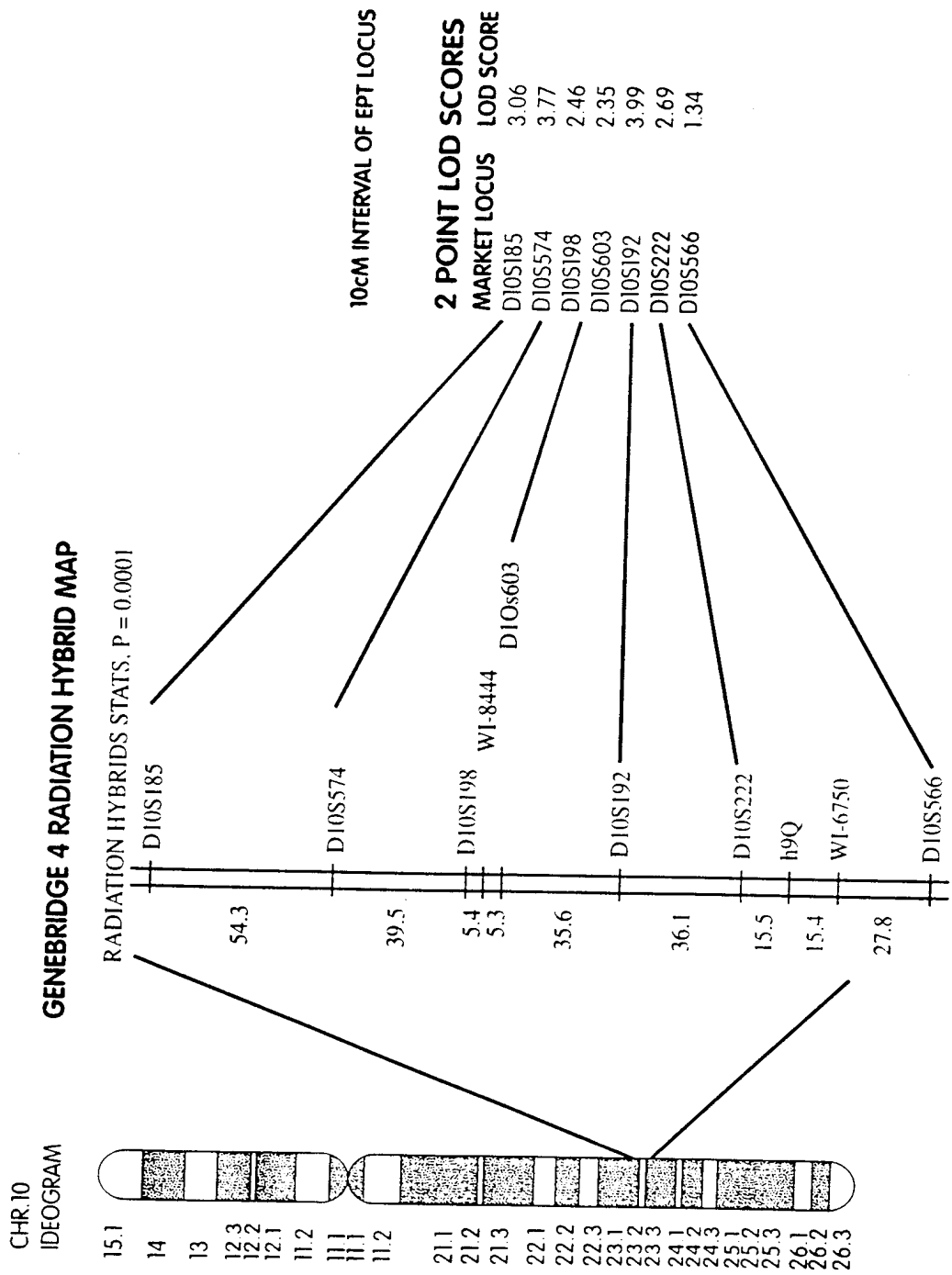


Fig. 43

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Arg	Pro	Ser	Lys	Asp	Lys	Ile	Glu	Asp	Glu	Leu	Glu	Met	Thr	Met	Val
			20					25					30		
Cys	His	Arg	Pro	Glu	Gly	Leu	Glu	Gln	Leu	Glu	Ala	Gln	Thr	Asn	Phe
		35				40						45			
Thr	Lys	Arg	Glu	Leu	Gln	Val	Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu	Cys
	50					55					60				
Pro	Ser	Gly	Val	Val	Asn	Glu	Asp	Thr	Phe	Lys	Gln	Ile	Tyr	Ala	Gln
65					70					75					80
Phe	Phe	Pro	His	Gly	Asp	Ala	Ser	Thr	Tyr	Ala	His	Tyr	Leu	Phe	Asn
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Ala	Phe	Asp	Thr	Thr	Gln	Thr	Gly	Ser	Val	Lys	Phe	Glu	Asp	Phe	Val
			100					105					110		
Thr	Ala	Leu	Ser	Ile	Leu	Leu	Arg	Gly	Thr	Val	His	Glu	Lys	Leu	Arg
		115					120					125			
Trp	Thr	Phe	Asn	Leu	Tyr	Asp	Ile	Asn	Lys	Asp	Gly	Tyr	Ile	Asn	Lys
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<211> 1856
<212> DNA
<213> Rattus sp.
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<221> CDS  
<222> (300)..(1034)
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ggggaaataa	aagcaaagat	taccatgaat	tgcaagatta	cctagcaatt	gcaaggtagg											180
aggagagagg	tggagggcgg	agtagacagg	agggagggag	aaagtgagag	gaagctaggc											240
tggttgaaat	aaccctgcac	ttggaacagc	ggcaaagaag	cgcgattttc	cagctttaa											299
atg	cct	gcc	cgc	gtt	ctg	ctt	gcc	tac	ccg	gga	acg	gag	atg	ttg	acc	347
Met	Pro	Ala	Arg	Val	Leu	Leu	Ala	Tyr	Pro	Gly	Thr	Glu	Met	Leu	Thr	
1				5					10					15		
cag	ggc	gag	tct	gaa	ggg	ctc	cag	acc	ttg	ggg	ata	gta	gtg	gtc	ctg	395
Gln	Gly	Glu	Ser	Glu	Gly	Leu	Gln	Thr	Leu	Gly	Ile	Val	Val	Val	Leu	
			20					25					30			
tgt	tcc	tct	ctg	aaa	cta	ctg	cac	tac	ctc	ggg	ctg	att	gac	ttg	tcg	443
Cys	Ser	Ser	Leu	Lys	Leu	Leu	His	Tyr	Leu	Gly	Leu	Ile	Asp	Leu	Ser	
		35					40					45				
gat	gac	aag	atc	gag	gat	gat	ctg	gag	atg	acc	atg	gtt	tgc	cat	cgg	491
Asp	Asp	Lys	Ile	Glu	Asp	Asp	Leu	Glu	Met	Thr	Met	Val	Cys	His	Arg	
	50					55					60					
cct	gag	gga	ctg	gag	cag	ctt	gag	gca	cag	acg	aac	ttc	acc	aag	aga	539
Pro	Glu	Gly	Leu	Glu	Gln	Leu	Glu	Ala	Gln	Thr	Asn	Phe	Thr	Lys	Arg	
65					70					75					80	
gaa	ctg	caa	gtc	ctt	tac	cgg	gga	ttc	aaa	aac	gag	tgc	ccc	agt	ggg	587
Glu	Leu	Gln	Val	Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu	Cys	Pro	Ser	Gly	
				85					90					95		

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gtg gtt aac gaa gag aca ttc aag cag atc tac gct cag ttt ttc cct 635
 Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro
 100 105 110

cat gga gat gcc agc aca tac gca cat tac ctc ttc aat gcc ttc gac 683
 His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp
 115 120 125

acc acc cag aca ggc tct gta aag ttc gag gac ttt gtg act gct ctg 731
 Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu
 130 135 140

tcg att tta ctg aga gga acg gtc cat gaa aaa ctg agg tgg acg ttt 779
 Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe
 145 150 155 160

aat ttg tac gac atc aat aaa gac ggc tac ata aac aaa gag gag atg 827
 Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met
 165 170 175

atg gac ata gtg aaa gcc atc tat gac atg atg ggg aaa tac acc tat 875
 Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
 180 185 190

cct gtg ctc aaa gag gac act ccc agg cag cac gtg gac gtc ttc ttc 923
 Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe
 195 200 205

cag aaa atg gat aaa aat aaa gat ggc att gta acg tta gac gaa ttt 971
 Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe
 210 215 220

ctc gag tcc tgt cag gag gat gac aac atc atg agg tct cta cag ctg 1019
 Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu
 225 230 235 240

ttc caa aat gtc atg taactgagga cactggccat cctgctctca gagacactga 1074
 Phe Gln Asn Val Met
 245

caaacacctc aatgccctga tctgcccttg ttccagtttt acacatcaac tctcgggaca 1134
 gaaatacctt ttacactttg gaagaattct ctgctgaaga ctttctacaa aacctggcac 1194
 cgagtggctc agtctctgat tgccaactct tcctccctcc tcctcttgag agggacgagc 1254
 tgaaatccga agtttgTTTT ggaagcatgc ccattctctcc atgctgctgc tgccctgtgg 1314
 aaggccccctc tgcttgagct taaacagtag tgcacagttt tctgcgtata cagatcccca 1374
 actcactgcc totaagtcag gcagaccctg atcaatctga accaaatgtg caccatcctc 1434
 cgatggcctc ccaagccaat gtgcctgctt ctcttctctt ggtgggaaga aagaacgctc 1494
 tacagagcac ttagagctta ccatgaaaat actgggagag gcagcaccta acacatgtag 1554
 aataggactg aattattaag catgggtggtg tcagatgatg caaacagccc atgtcatttt 1614
 tttttccaga ggtagggact aataattctc ccacactagc acctacgata atagaacaag 1674

tctttttaaca catccaggag ggaaccgct gccagtggt ctatcccttc tctccatccc 1734
 ctgctcaagc ccagcactgc atgtctctcc cggaagggtc agaatgcctg tgaaatgctg 1794
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 aa 1856

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 <212> PRT
 <213> Rattus sp.

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 20 25 30
 Cys Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile Asp Leu Ser
 35 40 45
 Asp Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val Cys His Arg
 50 55 60
 Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg
 65 70 75 80
 Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
 85 90 95
 Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro
 100 105 110
 His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp
 115 120 125
 Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu
 130 135 140
 Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe
 145 150 155 160
 Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met
 165 170 175
 Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
 180 185 190
 Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe
 195 200 205
 Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe
 210 215 220

- 7 -

Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu
 225 230 235 240

Phe Gln Asn Val Met
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<210> 5

<211> 1907

<212> DNA

<213> Mus musculus

<220>

<221> CDS

<222> (477)..(1124)

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 gcacgccggc cccgtgtcca acatcaggca ggctttgggg ctcggggctc gggcctcgga 180
 gaagccagtg gcccggctgg gtgcccgcac cggggggcgc ctgtgaaggc tcccgcgagc 240
 ctctggccct gggagtcagt gcatgtgcct ggctgaagaa ggcagcagcc acgagctcca 300
 ggcgccccgg cccacgttt tctgaatacc aagctgcagg cgagctgctc ggggcttttt 360
 tgctttctcg cttttcctct cctccaattc aaagtgggca atccacaccg atttcttttc 420
 aggggagggg agagacaggg cctgggggtcc caagacgcac acaagtcttc gctgcc atg 479
 Met
 1

ggg gcc gtc atg ggc act ttc tcc tcc ctg cag acc aaa caa agg cga 527
 Gly Ala Val Met Gly Thr Phe Ser Ser Leu Gln Thr Lys Gln Arg Arg
 5 10 15

ccc tct aaa gac aag att gag gat gag cta gag atg acc atg gtt tgc 575
 Pro Ser Lys Asp Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys
 20 25 30

cac cgg cct gag gga ctg gag cag ctt gag gca cag acg aac ttc acc 623
 His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr
 35 40 45

aag aga gaa ctg caa gtc ttg tac cgg gga ttc aaa aac gag tgc cct 671
 Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro
 50 55 60 65

agc ggt gtg gtc aat gaa gaa aca ttc aag cag atc tac gct cag ttt 719
 Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe
 70 75 80

ttc cct cac gga gat gcc agc aca tat gca cat tac ctc ttc aat gcc 767
 Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala

85	90	95	
ttc gac acc acc cag aca ggc tct gta aag ttc gag gac ttt gtg act			815
Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr			
100	105	110	
gct ctg tcg att tta ctg aga ggg aca gtc cat gaa aaa cta agg tgg			863
Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp			
115	120	125	
acg ttt aat ttg tat gac atc aat aaa gac ggc tac ata aac aaa gag			911
Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu			
130	135	140	145
gag atg atg gac ata gtc aaa gcc atc tat gac atg atg ggg aaa tac			959
Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr			
150	155	160	
acc tat cct gtg ctc aaa gag gac act ccc agg cag cat gtg gat gtc			1007
Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val			
165	170	175	
ttc ttc cag aaa atg gat aaa aat aaa gat ggc att gta acg tta gat			1055
Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp			
180	185	190	
gaa ttt ctt gaa tca tgt cag gag gat gac aac atc atg aga tct cta			1103
Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu			
195	200	205	
cag ctg ttc caa aat gtc atg taactgagga cactggccat tctgctctca			1154
Gln Leu Phe Gln Asn Val Met			
210	215		
gagacactga caaacacctt aatgccctga tctgcccttg ttccaatttt acacaccaac			1214
tcttgaggaca gaaatacctt ttacactttg gaagaattct ctgctgaaga ctttctacaa			1274
aacctggcac cacgtggctc tgtctctgag ggacgagcgg agatccgact ttgttttggga			1334
agcatgcca tctcttcatg ctgctgccct gtggaaggcc cctctgcttg agcttaatca			1394
atagtgcaca gttttatgct tacacatatc cccaactcac tgccctccaag tcaggcagac			1454
tctgatgaat ctgagccaaa tgtgcacccat cctccgatgg cctcccaagc caatgtgcct			1514
gcttctcttc ctctggtggg aagaaagagt gttctacgga acaattagag cttaccatga			1574
aaatattggg agaggcagca cctaacacat gtagaatagg actgaattat taagcatggt			1634
gatatcagat gatgcaaatt gcccatgtca tttttttcaa aggtagggac aaatgattct			1694
cccacactag cacctgtggt catagagcaa gtctcttaac atgcccagaa ggggaaccac			1754
tgtccagtgg tctatccctc ctctccatcc cctgctcaaa cccagcactg catgtccctc			1814
caagaaggct cagaatgcct gcgaaacgct gtacttttat accctgttct aatcaataaa			1874
cagaactatt tcgtaaaaaa aaaaaaaaaa aaa			1907

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<210> 6
 <211> 216
 <212> PRT
 <213> Mus musculus

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 Cys His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe
 35 40 45
 Thr Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys
 50 55 60
 Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln
 65 70 75 80
 Phe Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn
 85 90 95
 Ala Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val
 100 105 110
 Thr Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg
 115 120 125
 Trp Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys
 130 135 140
 Glu Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys
 145 150 155 160
 Tyr Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp
 165 170 175
 Val Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu
 180 185 190
 Asp Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser
 195 200 205
 Leu Gln Leu Phe Gln Asn Val Met
 210 215

<210> 7
 <211> 1534
 <212> DNA
 <213> Rattus sp.

<220>
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 <222> (31)..(711)

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tcg tcc ctg cag acc aaa caa agg cga ccc tct aaa gac atc gcc tgg 102
Ser Ser Leu Gln Thr Lys Gln Arg Arg Pro Ser Lys Asp Ile Ala Trp
10 15 20

tgg tat tac cag tat cag aga gac aag atc gag gat gat ctg gag atg 150
Trp Tyr Tyr Gln Tyr Gln Arg Asp Lys Ile Glu Asp Asp Leu Glu Met
25 30 35 40

acc atg gtt tgc cat cgg cct gag gga ctg gag cag ctt gag gca cag 198
Thr Met Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln
45 50 55

acg aac ttc acc aag aga gaa ctg caa gtc ctt tac cgg gga ttc aaa 246
Thr Asn Phe Thr Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys
60 65 70

aac gag tgc ccc agt ggt gtg gtt aac gaa gag aca ttc aag cag atc 294
Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile
75 80 85

tac gct cag ttt ttc cct cat gga gat gcc agc aca tac gca cat tac 342
Tyr Ala Gln Phe Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr
90 95 100

ctc ttc aat gcc ttc gac acc acc cag aca ggc tct gta aag ttc gag 390
Leu Phe Asn Ala Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu
105 110 115 120

gac ttt gtg act gct ctg tcg att tta ctg aga gga acg gtc cat gaa 438
Asp Phe Val Thr Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu
125 130 135

aaa ctg agg tgg acg ttt aat ttg tac gac atc aat aaa gac ggc tac 486
Lys Leu Arg Trp Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr
140 145 150

ata aac aaa gag gag atg atg gac ata gtg aaa gcc atc tat gac atg 534
Ile Asn Lys Glu Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met
155 160 165

atg ggg aaa tac acc tat cct gtg ctc aaa gag gac act ccc agg cag 582
Met Gly Lys Tyr Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln
170 175 180

cac gtg gac gtc ttc ttc cag aaa atg gat aaa aat aaa gat ggc att 630
His Val Asp Val Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile
185 190 195 200

gta acg tta gac gaa ttt ctc gag tcc tgt cag gag gat gac aac atc 678
Val Thr Leu Asp Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile
205 210 215

- 11 -

atg agg tct cta cag ctg ttc caa aat gtc atg taactgagga cactggccat 731
 Met Arg Ser Leu Gln Leu Phe Gln Asn Val Met
 220 225

cctgctctca gagacactga caaacacctc aatgccctga tctgcccttg ttccagtttt 791
 acacatcaac tctcgggaca gaaatacctt ttacactttg gaagaattct ctgctgaaga 851
 ctttctacaa aacctggcac cgcgtggctc agtctctgat tgccaactct tectccctcc 911
 tctctttgag agggacgagc tgaaatccga agtttgtttt ggaagcatgc ccatctctcc 971
 atgctgctgc tgccctgtgg aaggccctc tgcttgagct taaacagtag tgcacagttt 1031
 tctgctgata cagatcccca actcactgcc tctaagtcag gcagaccctg atcaatctga 1091
 accaaatgtg caccatcctc cgatggcctc ccaagccaat gtgcctgctt ctcttctctt 1151
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 gcagcaccta acacatgtag aataggactg aattattaag catggtggta tcagatgatg 1271
 caaacagccc atgtcatttt ttttccagag gtagggacta ataattctcc cacactagca 1331
 cctacgatca tagaacaagt cttttaacac atccaggagg gaaaccgctg cccagtggctc 1391
 tatcccttct ctccatcccc tgetcaagcc cagcactgca tgtctctccc ggaaggtcca 1451
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 <212> PRT
 <213> Rattus sp.

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 20 25 30
 Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val Cys His Arg Pro Glu
 35 40 45
 Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu Leu
 50 55 60
 Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val
 65 70 75 80
 Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro His Gly
 85 90 95
 Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr Thr
 100 105 110

Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser Ile
 115 120 125
 Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe Asn Leu
 130 135 140
 Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met Asp
 145 150 155 160
 Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Val
 165 170 175
 Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe Gln Lys
 180 185 190
 Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe Leu Glu
 195 200 205
 Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu Phe Gln
 210 215 220
 Asn Val Met
 225

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 <212> DNA
 <213> Mus musculus

 <220>
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 <222> (77)..(757)

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 Met Gly Ala Val Met Gly Thr Phe Ser Ser Leu Gln
 1 5 10
 acc aaa caa agg cga ccc tct aaa gac atc gcc tgg tgg tat tac cag 160
 Thr Lys Gln Arg Arg Pro Ser Lys Asp Ile Ala Trp Trp Tyr Tyr Gln
 15 20 25
 tat cag aga gac aag att gag gat gag cta gag atg acc atg gtt tgc 208
 Tyr Gln Arg Asp Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys
 30 35 40
 cac cgg cct gag gga ctg gag cag ctt gag gca cag acg aac ttc acc 256
 His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr
 45 50 55 60
 aag aga gaa ctg caa gtc ttg tac cgg gga ttc aaa aac gag tgc cct 304
 Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro
 65 70 75
 agc ggt gtg gtc aat gaa gaa aca ttc aag cag atc tac gct cag ttt 352

Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe
80 85 90

ttc cct cac gga gat gcc agc aca tat gca cat tac ctc ttc aat gcc 400
Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala
95 100 105

ttc gac acc acc cag aca ggc tct gta aag ttc gag gac ttt gtg act 448
Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr
110 115 120

gct ctg tcg att tta ctg aga ggg aca gtc cat gaa aaa cta agg tgg 496
Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp
125 130 135 140

acg ttt aat ttg tat gac atc aat aaa gac ggc tac ata aac aaa gag 544
Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu
145 150 155

gag atg atg gac ata gtc aaa gcc atc tat gac atg atg ggg aaa tac 592
Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr
160 165 170

acc tat cct gtg ctc aaa gag gac act ccc agg cag cat gtg gat gtc 640
Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val
175 180 185

ttc ttc cag aaa atg gat aaa aat aaa gat ggc att gta acg tta gat 688
Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp
190 195 200

gaa ttt ctt gaa tca tgt cag gag gat gac aac atc atg aga tct cta 736
Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu
205 210 215 220

cag ctg ttc caa aat gtc atg taactgagga cactggccat tctgctctca 787
Gln Leu Phe Gln Asn Val Met
225

gagacactga caaacacctt aatgccctga tctgcccttg ttccaatttt acacaccaac 847

tcttgggaca gaaatacctt ttacactttg gaagaattct ctgctgaaga ctttctacaa 907

aacctggcac cacgtggctc tgtctctgag ggacgagcgg agatccgact ttgttttggg 967

agcatgcccc tctcttcatg ctgctgccct gtggaaggcc cctctgcttg agcttaatca 1027

atagtgcaca gttttatgct tacacatatc cccaactcac tgccctccaag tcaggcagac 1087

tctgatgaat ctgagccaaa tgtgcaccat cctccgatgg cctcccaagc caatgtgcct 1147

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- 14 -

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 Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu Leu
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 Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val
 65 70 75 80
 Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro His Gly
 85 90 95
 Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr Thr
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 Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser Ile
 115 120 125
 Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe Asn Leu
 130 135 140
 Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met Asp
 145 150 155 160
 Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Val
 165 170 175
 Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe Gln Lys
 180 185 190
 Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe Leu Glu
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 <222> (345)..(953)

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 sequence may be any amino acid

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 Met Leu Thr Gln
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 Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile Asp Leu Ser Asp
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 40 45 50
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 Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu
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 ctg caa gtc ctt tac cgg gga ttc aaa aac gag tgc ccc agt ggt gtg 596
 Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val
 70 75 80
 gtt aac gaa gag aca ttc aag cng atc tac gct cag ttt ttc cct cat 644
 Val Asn Glu Glu Thr Phe Lys Xaa Ile Tyr Ala Gln Phe Phe Pro His
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 Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr
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 acc cag aca ggc tct gta aag ttc gag gac ttt gtg act gct ctg tcg 740

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 135 140 145
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 Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met
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 gac ata gtg aaa gcc atc tat gac atg atg ggg aaa tac acc tat ctt 884
 Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Leu
 165 170 175 180
 gtg ctc aaa gag gac act tcc agg cag cac gtg gac gtc ttc ttc cag 932
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 Thr Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys
 65 70 75 80
 Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Xaa Ile Tyr Ala Gln
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 Phe Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn
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 115 120 125
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Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr
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tta gcc gcc cca gcc tcc ctg cgc ccc cac aga ccc cgc ctg ctg gac 425
Leu Ala Ala Pro Ala Ser Leu Arg Pro His Arg Pro Arg Leu Leu Asp
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Pro Asp Ser Val Asp Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg
75 80 85

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Pro Glu Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys
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ctt gac atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac 857
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Arg Pro His Arg Pro Arg Leu Leu Asp Pro Asp Ser Val Asp Asp Glu
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Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
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Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg
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Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
 115 120 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr
 130 135 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
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Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr
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Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
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Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
 210 215 220

Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
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Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp
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tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aca tta gct gcc cca 145
 Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro
 35 40 45

gcc tcc ctc cgc ccc cac aga ccc cgc ccg ctg gac cca gac agc gta 193
 Ala Ser Leu Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val
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gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag ggc ctg 241
 Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
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gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg cag gtc 289
 Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
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ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc aac gag 337
 Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
 100 105 110

gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga gac tcc 385
 Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
 115 120 125

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 Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
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 aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc ctc cgg 625
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 Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
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 100 105 110
 Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
 115 120 125
 Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
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 Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
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 Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
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 195 200 205
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<222> (181)..(990)

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caa gcc ctg ccc tca gtc agt gaa aca tta gct gcc cca gcc tcc ctc      372
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Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
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cag gaa caa acc aag ttc aca cgc aga gag ttg cag gtc ctg tac aga      516
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Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
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aag caa att tat tct cag ttc ttt ccc caa gga gac tcc agc aac tac      612
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<212> PRT

<213> Mus musculus

<400> 18

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Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
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Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val Glu Asp Glu
 65 70 75 80

Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
 85 90 95

Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg
 100 105 110

Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
 115 120 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr
 130 135 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
 145 150 155 160

Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr
 165 170 175

Ile Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
 180 185 190

Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile
 195 200 205

Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
 210 215 220

Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
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 <213> Homo sapiens

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 <222> (207)..(962)

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 Met Arg Gly Gln Gly Arg Lys Glu Ser
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 His Pro Pro Gly Pro Thr Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys
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 ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac 377
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 agc gtg gac gat gaa ttt gaa ttg tcc acc gtg tgt cac cgg cct gag 425
 Ser Val Asp Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu
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 ggt ctg gag cag ctg cag gag caa acc aaa ttc acg cgc aag gag ttg 473
 Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu
 75 80 85
 cag gtc ctg tac cgg ggc ttc aag aac gaa tgt ccc agc gga att gtc 521
 Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val
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 Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly
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 Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn
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 cat gat ggc tcg gtc agt ttt gag gac ttt gtg gct ggt ttg tcc gtg 665

His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val
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 Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp
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atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac cct gca 809
 Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala
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ctc cgg gag gag gcc cca agg gaa cac gtg gag agc ttc ttc cag aag 857
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 205 210 215

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 220 225 230

tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctc ttt gac 953
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 235 240 245

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 Asn Val Ile
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<212> PRT

<213> Homo sapiens

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Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
 85 90 95

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
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Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
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Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
 130 135 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
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Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
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Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
 180 185 190

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 195 200 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
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 <222> (214)..(969)

<400> 21

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Glu Ser Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu
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Thr Gly His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe
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cct gag ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga 474
Pro Glu Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg
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 170 175 180

ctt gac att atg aag tcc atc tat gac atg atg ggc aag tac aca tac 810
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cct gcc ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc 858
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 200 205 210 215

cag aag atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc 906
 Gln Lys Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe
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atc gag tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc 954
 Ile Glu Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu
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 Phe Asp Asn Val Ile
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<213> Rattus sp.

<400> 22

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Lys	Ala	Leu	Lys	Gln	Arg	Phe	Leu	Lys	Leu	Leu	Pro	Cys	Cys	Gly	Pro
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Phe	Leu	Phe	Asn	Ala	Phe	Asp	Thr	Asn	His	Asp	Gly	Ser	Val	Ser	Phe
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Asp	Arg	Leu	Ser	Trp	Ala	Phe	Asn	Leu	Tyr	Asp	Leu	Asn	Lys	Asp	Gly
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Cys	Ile	Thr	Lys	Glu	Glu	Met	Leu	Asp	Ile	Met	Lys	Ser	Ile	Tyr	Asp
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Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
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Ser	Val	Asp	Asp	Glu	Phe	Glu	Leu	Ser	Thr	Val	Cys	His	Arg	Pro	Glu	
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Gly	Leu	Glu	Gln	Leu	Gln	Glu	Gln	Thr	Lys	Phe	Thr	Arg	Lys	Glu	Leu	
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cag	gtc	ctg	tac	cgg	ggc	ttc	aag	aac	gaa	tgt	ccc	agc	gga	att	gtc	425
Gln	Val	Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu	Cys	Pro	Ser	Gly	Ile	Val	
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Asn	Glu	Glu	Asn	Phe	Lys	Gln	Ile	Tyr	Ser	Gln	Phe	Phe	Pro	Gln	Gly	
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gac	tcc	agc	acc	tat	gcc	act	ttt	ctc	ttc	aat	gcc	ttt	gac	acc	aac	521
Asp	Ser	Ser	Thr	Tyr	Ala	Thr	Phe	Leu	Phe	Asn	Ala	Phe	Asp	Thr	Asn	
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 170 175 180 185

atg gac aga aac aag gat ggt gtg gtg acc att gag gaa ttc att gag 809
 Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu
 190 195 200

tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctc ttt gac 857
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 205 210 215

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 Asn Val Ile
 220

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 Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
 50 55 60
 Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
 65 70 75 80
 Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
 85 90 95
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 Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
 115 120 125
 Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
 130 135 140
 Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
 145 150 155 160
 Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
 165 170 175
 Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
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Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Asp Ser Val Glu Asp
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Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln
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Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr
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Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser
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Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu
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<213> Simian sp.

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 Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
 115 120 125
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 Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
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 Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
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 Glu His Val Glu Asn Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
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<212> DNA

<213> Simian sp.

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gccgccaggg ggcgctgtgt gagcgcctta ttctggccac ccggcgcccc ctcccacggc 180

220 225 230
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 Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Ser Pro
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 Leu Leu Asn
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 <213> Simian sp.

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- 40 -

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 Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
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 100 105 110
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 Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
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 <213> Rattus sp.

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 <221> CDS
 <222> (1)..(675)

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 Arg Ser Leu Tyr Gln Leu Val Thr Gly Ser Leu Ser Pro Asp Ser Val

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ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc aac gag			240
Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu			
65	70	75	80
gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga gac tcc			288
Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser			
85	90	95	
agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac cac gat			336
Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp			
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Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu			
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Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp			
130	135	140	
ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac att atg			480
Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met			
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Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp			
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Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys			
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225			
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<211> 225

<212> PRT

<213> Rattus sp.

<400> 30

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Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu	Cys	Pro	Ser	Gly	Ile	Val	Asn	Glu
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Glu	Asn	Phe	Lys	Gln	Ile	Tyr	Ser	Gln	Phe	Phe	Pro	Gln	Gly	Asp	Ser
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1				5					10					15		
ggg	gac	ctc	ggg	cac	aca	cca	ctt	agc	aag	aag	gag	ggt	atc	aag	tgg	96
Gly	Asp	Leu	Gly	His	Thr	Pro	Leu	Ser	Lys	Lys	Glu	Gly	Ile	Lys	Trp	
			20					25					30			
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Gln	Arg	Pro	Arg	Leu	Ser	Arg	Gln	Ala	Leu	Met	Arg	Cys	Cys	Leu	Val	
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Lys	Trp	Ile	Leu	Ser	Ser	Thr	Ala	Pro	Gln	Gly	Ser	Asp	Ser	Ser	Asp	
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Ser	Glu	Leu	Glu	Leu	Ser	Thr	Val	Arg	His	Gln	Pro	Glu	Gly	Leu	Asp	
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 Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
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 115 120 125

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 Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
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 225 230 235 240

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<212> PRT

<213> Homo sapiens

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Gly  Asp  Leu  Gly  His  Thr  Pro  Leu  Ser  Lys  Lys  Glu  Gly  Ile  Lys  Trp
                20              25              30

Gln  Arg  Pro  Arg  Leu  Ser  Arg  Gln  Ala  Leu  Met  Arg  Cys  Cys  Leu  Val
                35              40              45

Lys  Trp  Ile  Leu  Ser  Ser  Thr  Ala  Pro  Gln  Gly  Ser  Asp  Ser  Ser  Asp
                50              55              60

Ser  Glu  Leu  Glu  Leu  Ser  Thr  Val  Arg  His  Gln  Pro  Glu  Gly  Leu  Asp
 65              70              75              80

Gln  Leu  Gln  Ala  Gln  Thr  Lys  Phe  Thr  Lys  Lys  Glu  Leu  Gln  Ser  Leu
                85              90              95

Tyr  Arg  Gly  Phe  Lys  Asn  Glu  Cys  Pro  Thr  Gly  Leu  Val  Asp  Glu  Asp
                100              105              110

Thr  Phe  Lys  Leu  Ile  Tyr  Ala  Gln  Phe  Phe  Pro  Gln  Gly  Asp  Ala  Thr
                115              120              125

Thr  Tyr  Ala  His  Phe  Leu  Phe  Asn  Ala  Phe  Asp  Ala  Asp  Gly  Asn  Gly
 130              135              140

Ala  Ile  His  Phe  Glu  Asp  Phe  Val  Val  Gly  Leu  Ser  Ile  Leu  Leu  Arg
145              150              155              160

Gly  Thr  Val  His  Glu  Lys  Leu  Lys  Trp  Ala  Phe  Asn  Leu  Tyr  Asp  Ile
                165              170              175

Asn  Lys  Asp  Gly  Tyr  Ile  Thr  Lys  Glu  Glu  Met  Leu  Ala  Ile  Met  Lys
                180              185              190

Ser  Ile  Tyr  Asp  Met  Met  Gly  Arg  His  Thr  Tyr  Pro  Ile  Leu  Arg  Glu
                195              200              205

Asp  Ala  Pro  Ala  Glu  His  Val  Glu  Arg  Phe  Phe  Glu  Lys  Met  Asp  Arg
 210              215              220

Asn  Gln  Asp  Gly  Val  Val  Thr  Ile  Glu  Glu  Phe  Leu  Glu  Ala  Cys  Gln
225              230              235              240

Lys  Asp  Glu  Asn  Ile  Met  Ser  Ser  Met  Gln  Leu  Phe  Glu  Asn  Val  Ile
                245              250              255

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<210> 33

<211> 442

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1)..(327)

<400> 33

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ttt gag gac ttt gtg gtt ggg ctc tcc atc ctg ctt cga ggg acc gtc      48
Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
  1                      5                      10                      15

cat gag aag ctc aag tgg gcc ttc aat ctc tac gac atc aac aag gac      96
His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
                20                      25                      30

ggt tac atc acc aaa gag gag atg ctg gcc atc atg aag tcc atc tac      144
Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
                35                      40                      45

gac atg atg ggc cgc cac acc tac cct atc ctg cgg gag gac gca cct      192
Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
                50                      55                      60

ctg gag cat gtg gag agg ttc ttc cag aaa atg gac agg aac cag gat      240
Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
        65                      70                      75                      80

gga gta gtg act att gat gaa ttt ctg gag act tgt cag aag gac gag      288
Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu
                85                      90                      95

aac atc atg agc tcc atg cag ctg ttt gag aac gtc atc taggacatgt      337
Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
                100                      105

aggagggggac cctgggtggc catgggttct caaccagag aagcctcaat cctgacagga 397

gaagcctcta tgagaaacat ttttctaata tatttgcaaa aagtg      442

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<210> 34

<211> 109

<212> PRT

<213> Rattus sp.

<400> 34

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Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
  1                      5                      10                      15

His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
                20                      25                      30

Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
                35                      40                      45

Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
                50                      55                      60

Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
        65                      70                      75                      80

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<400> 35																
cgggctgcaa agcgggaaga ttagtgacgg tcccttttcag cagcagag atg cag agg																57
Met Gln Arg																
1																
acc aag gaa gcc gtg aag gca tca gat ggc aac ctg ctg gga gat cct																105
Thr Lys Glu Ala Val Lys Ala Ser Asp Gly Asn Leu Leu Gly Asp Pro																
5 10 15																
ggg cgc ata cca ctg agc aag agg gaa agc atc aag tgg caa agg cca																153
Gly Arg Ile Pro Leu Ser Lys Arg Glu Ser Ile Lys Trp Gln Arg Pro																
20 25 30 35																
cgg ttc acc cgc cag gcc ctg atg cgt tgc tgc tta atc aag tgg atc																201
Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile Lys Trp Ile																
40 45 50																
ctg tcc agt gct gcc cca caa ggc tca gac agc agt gac agt gaa ctg																249
Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Ser Asp Ser Glu Leu																
55 60 65																
gag tta tcc acg gtg cgc cat cag cca gag ggc ttg gac cag cta caa																297
Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp Gln Leu Gln																
70 75 80																
gct cag acc aag ttc acc aag aag gag ctg cag tcc ctt tac cga ggc																345
Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu Tyr Arg Gly																
85 90 95																
ttc aag aat gag tgt ccc aca ggc ctg gtg gat gaa gac acc ttc aaa																393
Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp Thr Phe Lys																
100 105 110 115																
ctc att tat tcc cag ttc ttc cct cag gga gat gcc acc acc tat gca																441
Leu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ala Thr Thr Tyr Ala																
120 125 130																
cac ttc ctc ttc aat gcc ttt gat gct gat ggg aac ggg gcc atc cac																489
His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly Ala Ile His																
135 140 145																
ttt gag gac ttt gtg gtt ggg ctc tcc atc ctg ctt cga ggg acg gtc																537
Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val																

150	155	160	
cat gag aag ctc aag tgg gcc ttc aat ctc tat gac att aac aag gat			585
His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp			
165	170	175	
ggt tgc atc acc aag gag gag atg ctg gcc atc atg aag tcc atc tac			633
Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr			
180	185	190	195
gac atg atg ggc cgc cac acc tac ccc atc ctg cgg gag gat gca ccc			681
Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro			
	200	205	210
ctg gag cat gtg gag agg ttc ttt cag aaa atg gac agg aac cag gat			729
Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp			
	215	220	225
gga gtg gtg acc att gat gaa ttt ctg gag act tgt cag aag gat gag			777
Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu			
	230	235	240
aac atc atg aac tcc atg cag ctg ttt gag aac gtc atc taggacatgt			826
Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile			
	245	250	255
gggaggggac cccagtggtc attgcttctc aaccagaga agcctcaatc ctgacaggag			886
aagcctctat gagaaacatt tttctaatat atttgcaaaa agtgagcagt ttacttccaa			946
gacacagcca ccgtcacaca cagacacaga catacagaca cacacacaca cacacacaca			1006
tggttcctct ggcttggcca aggaagtggc agccagaagg caccctcgcc tattcctagg			1066
tcaataaaaa aggctgcctc tgggatggcc agcctgggt agatgttacc cacaaggaac			1126
tcagagatcg agaggaccag gtctacaaaag ctaagggtccc tgtgtctttt ctaccactcg			1186
ggagatcaaa ctactccctg cctatggacc catgctctta ggaagctccc agaaactcca			1246
aggggacaaa gaggggagag gtctatagga agaaatgggt ttggaagctg ggcttgcagc			1306
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gagcttagat agtgaggggc cattggacta agacctctg taagagtggg gcaggattga			1426
ggtttttgga gaaactgagg aaacaatttg tccataccac tgggtgaaga ctgctggcca			1486
gtgggaatgt ggctgggtgga gatttcccaa cttccagcac caggatggcc tctccaaggt			1546
cctctttgat tccctgggga gatcacctgg ctcatagact gacaaccagg gaactgggct			1606
gaaatgggag gtctggtagg gggcatcccc ctctttttcc ctggccactt gccaccagt			1666
tccttaacac agtggatcgg ccacacctct gtggctgccc ttgaacagac tcatcccgac			1726
caagacaaaa aagcacaac tctagcagc tcaggccaag cccacaaggg aaggcctggg			1786
tccctgcagc cctgattcag tggccgagga agacgctcag acatccatcc tgtacctcg			1846


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agccttgggg gtctcacagc cctttcccag cccagctcgc caacattcta aagcacaaac 1906
ctgcgggattc tgccttgcttg ggctgcgccc tggggattga aggccactgt taaccctaag 1966
ctggagctag cctgaggggc tggggacctg tgaccaggca acaggtcagc agaccctcag 2026
gaggagagag agctgttcct gcctccccag gcctcgccca gaaggaacag tgtcccaaga 2086
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<210> 36

<211> 256

<212> PRT

<213> Mus musculus

<400> 36

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Met Gln Arg Thr Lys Glu Ala Val Lys Ala Ser Asp Gly Asn Leu Leu
  1             5             10             15
Gly Asp Pro Gly Arg Ile Pro Leu Ser Lys Arg Glu Ser Ile Lys Trp
             20             25             30
Gln Arg Pro Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile
             35             40             45
Lys Trp Ile Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Ser Asp
             50             55             60
Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
             65             70             75             80
Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
             85             90             95
Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
             100            105            110
Thr Phe Lys Leu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ala Thr

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- 51 -

115	120	125
Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly		
130	135	140
Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg		
145	150	155
Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile		
165	170	175
Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys		
180	185	190
Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu		
195	200	205
Asp Ala Pro Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg		
210	215	220
Asn Gln Asp Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln		
225	230	235
Lys Asp Glu Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile		
245	250	255

<210> 37

<211> 531

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(336)

<220>

<223> At position 495, n=any amino acid

<400> 37

cac gag gtg gaa agc att tcg gct cag ctg gag gag gcc agc tct aca	48
His Glu Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala Ser Ser Thr	
1	5
ggc ggt ttc ctg tac gct cag aac agc acc aag cgc agc att aaa gag	96
Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu	
20	25
cgg ctc atg aag ctc ttg ccc tgc tca gct gcc aaa acg tcg tct cct	144
Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro	
35	40
gct att caa aac agc gtg gaa gat gaa ctg gag atg gcc acc gtc agg	192
Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg	
50	55
cat cgg ccc gaa gcc ctt gag ctt ctg gaa gcc cag agc aaa ttt acc	240
His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr	
65	70
	75
	80

aag aaa gag ctt cag atc ctt tac aga gga ttt aag aac gta aga act 288
 Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
 85 90 95

ttc ttt ttg act tta cct tca cac aat tcc cag agg agc att gag aaa 336
 Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
 100 105 110

tgagaggaaa aggggggaaaa tatcccatc tatgagaagc cccatcatat gtatatttca 396

tactgatcct tccagatag gaatataatc agtatctgtg gactttgaa ctctgtggca 456

cacccatgct ggcatactgt aattgcccat taaacaaana gtttttgaga aaaaaaaaaa 516

aaaaaaaaaa aaaaaa 531

<210> 38

<211> 112

<212> PRT

<213> Homo sapiens

<400> 38

His Glu Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala Ser Ser Thr
 1 5 10 15

Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu
 20 25 30

Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro
 35 40 45

Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg
 50 55 60

His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr
 65 70 75 80

Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
 85 90 95

Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
 100 105 110

<210> 39

<211> 2176

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (2)..(124)

<400> 39

t gaa agg ttc ttc gag aaa atg gac cgg aac cag gat ggg gta gtg acc 49
 Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
 1 5 10 15

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att gaa gag ttc ctg gag gcc tgt cag aag gat gag aac atc atg agc 97
Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
      20                      25                      30

tcc atg cag ctg ttt gag aat gtc atc taggacacgt ccaaaggagt 144
Ser Met Gln Leu Phe Glu Asn Val Ile
      35                      40

gcatggccac agccacctcc accccaaga aacctccatc ctgccaggag cagcctccaa 204
gaaacttttta aaaaatagat ttgcaaaaag tgaacagatt gctacacaca cacacacaca 264
cacacacaca cacacacaca cacagccatt catctgggct ggcagagggg acagagttca 324
gggaggggct gagtctggct aggggccgag tccaggagcc ccagccagcc cttcccaggc 384
cagcgaggcg aggctgcctc tgggtgagtg gctgacagag caggtctgca ggccaccagc 444
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gagagatgct gctccgcct gattggggcc tcaccagaa ggaaccgggt ccaggccgc 1584
atggccctc caggaacatt cccacataat acattccatc acagccagcc cagctccact 1644

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- 54 -

cagggctggc cgggggagtc cccgtgtgcc ccaagaggct agccccaggg tgagcagggc 1704
 cctcagagga aaggcagtat ggcggaggcc atggggggccc ctgggcattc acacacagcc 1764
 tggcctcccc tgcggagctg catggacgcc tggctccagg ctccaggctg actggggggc 1824
 tctgcctcca ggagggcacc agctttccct ggctcaggga ttttctccct cccctcacc 1884
 gctgcccagc cctcccagct ggtgtcactc tgcctctaag gccaaaggcct caggagagca 1944
 tcaccaccac acccctgccg gccttggcct tggggccaga ctggctgcac agcccaacca 2004
 ggaggggtct gcctcccacg ctgggacaca gaccggccgc atgtctgcat ggcagaagcg 2064
 tctcccttgg ccacggcctg ggaggggtgt tctgtttctc agcatccact aatattcagt 2124
 cctgtatatt ttaataaaat aaacttgaca aaggaaaaaa aaaaaaaaaa aa 2176

<210> 40

<211> 41

<212> PRT

<213> Homo sapiens

<400> 40

Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
 1 5 10 15

Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
 20 25 30

Ser Met Gln Leu Phe Glu Asn Val Ile
 35 40

<210> 41

<211> 2057

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (208)..(963)

<400> 41

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 gccgccaggg ggcgctgtgt gagcgcccta ttctggccac ccggcgcccc ctcccacggc 180
 ccaggcggga gcggggcgcc gggggcc atg cgg ggc caa ggc aga aag gag agt 234
 Met Arg Gly Gln Gly Arg Lys Glu Ser
 1 5
 ttg tcc gaa tcc cga gat ctg gac ggc tcc tat gac cag ctt acg ggc 282
 Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10 15 20 25

cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag	330
His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys	
30 35 40	
ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac	378
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn	
45 50 55	
agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag	426
Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu	
60 65 70	
ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg	474
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu	
75 80 85	
cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc	522
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val	
90 95 100 105	
aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga	570
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly	
110 115 120	
gac tcc agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac	618
Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn	
125 130 135	
cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg	666
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val	
140 145 150	
att ctt cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta	714
Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu	
155 160 165	
tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac	762
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp	
170 175 180 185	
att atg aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc	810
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala	
190 195 200	
ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag	858
Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys	
205 210 215	
atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag	906
Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu	
220 225 230	
tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc tca ccc	954
Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Ser Pro	
235 240 245	
ctt ctc aac tgatacctag tgctgaggac acccctggtg tagggaccaa	1003
Leu Leu Asn	
250	

gtggttctcc accttctagt cccactctag aaaccacatt agacagaagg tctcctgcta 1063
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 ggttccgggg cctacagccc tgggtcagca gagtatgagt tcccagactt tccagaaggt 1363
 ccttagcaat gtcccagaaa ttcaccgtac acttctcagt gtcttaggag ggcccgggat 1423
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 tggccagggg aagatgagt gtgtcccgga tgatgcctgt caaggtecca cctcccctcc 1543
 ggctgttctc atgacagctg tttgggttct catgaccctt atctagatgt agaggcatgg 1603
 agtgagtcag ggatttcccg aacttgagtt ttaccactcc tctagtggc tgccttaggg 1663
 gaatgggaag aaccagtggt gggggcacc attagaatct ttgccgggt cctcacaatg 1723
 ccctaggggc ccctagggta cccgctcct ctgttttagtc taccagaga tgctcctgag 1783
 ctcacctaga gggtagggac ggtaggctcc aggtccaacc tctccaggtc agcaccctgc 1843
 catgctgctg ctctcatta acaaacctgc ttgtctctc ctgcgcccct tctcagtcag 1903
 ccagggctct aggggaagg cctcccgttt cccatccgt cagacatggg tgactgcttt 1963
 gcattttggg ctcttctatc tattttgtaa aataagacat cagatccaat aaaacacacg 2023
 gctatgcaca aaaaaaaaaa aaaaaaaaaa aaaa 2057

<210> 42

<211> 252

<212> PRT

<213> Rattus sp.

<400> 42

Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
 1 5 10 15

Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
 20 25 30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
 35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
 50 55 60

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
 65 70 75 80

- 57 -

Gln	Thr	Lys	Phe	Thr	Arg	Arg	Glu	Leu	Gln	Val	Leu	Tyr	Arg	Gly	Phe
				85						90					95
Lys	Asn	Glu	Cys	Pro	Ser	Gly	Ile	Val	Asn	Glu	Glu	Asn	Phe	Lys	Gln
			100					105					110		
Ile	Tyr	Ser	Gln	Phe	Phe	Pro	Gln	Gly	Asp	Ser	Ser	Asn	Tyr	Ala	Thr
		115					120					125			
Phe	Leu	Phe	Asn	Ala	Phe	Asp	Thr	Asn	His	Asp	Gly	Ser	Val	Ser	Phe
	130					135					140				
Glu	Asp	Phe	Val	Ala	Gly	Leu	Ser	Val	Ile	Leu	Arg	Gly	Thr	Ile	Asp
145					150					155					160
Asp	Arg	Leu	Ser	Trp	Ala	Phe	Asn	Leu	Tyr	Asp	Leu	Asn	Lys	Asp	Gly
				165					170					175	
Cys	Ile	Thr	Lys	Glu	Glu	Met	Leu	Asp	Ile	Met	Lys	Ser	Ile	Tyr	Asp
			180					185					190		
Met	Met	Gly	Lys	Tyr	Thr	Tyr	Pro	Ala	Leu	Arg	Glu	Glu	Ala	Pro	Arg
		195					200					205			
Glu	His	Val	Glu	Ser	Phe	Phe	Gln	Lys	Met	Asp	Arg	Asn	Lys	Asp	Gly
	210					215					220				
Val	Val	Thr	Ile	Glu	Glu	Phe	Ile	Glu	Ser	Cys	Gln	Gln	Asp	Glu	Asn
225					230					235					240
Ile	Met	Arg	Ser	Met	Gln	Leu	Ser	Pro	Leu	Leu	Asn				
				245					250						

<210> 43

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Xaas at positions 2,5,6,9,17,25 and 26 may be Ile,
Leu, Val or Met

 $\langle 220 \rangle$

<223> Xaas at positions 3,4,7,8,16,18-20,23 and 24 may
be any amino acid

 $\langle 220 \rangle$

<223> Description of Artificial Sequence: consensus motif

<400> 43

Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Lys Asp Gly Asp Gly Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Glu Phe Xaa Xaa Xaa Xaa
20 25


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<210> 45
<211> 40
<212> DNA
<213> Rattus sp.
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<210> 46
<211> 40
<212> DNA
<213> Rattus sp.
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<210> 47
<211> 40
<212> DNA
<213> Rattus sp.
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<210> 48
<211> 2413
<212> DNA
<213> Simian sp.
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<400> 48
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ggatcagcat gagaggctg acttttagtcc aggtctgtcc tcaccccggtt ggaccgccgg 120
ctttgcaggg tgcagctgcg aggaactgct cacttttttc cccttgcaag tctttgttcc 180
aagcctgacg ttgctacgat tctgtaatta actccctcca ctccaaaggg gtctggaggc 240
tgggatgctc tgccagctca gagg atg ttg act ctg gag tgg gag tcc gaa 291
          Met Leu Thr Leu Glu Trp Glu Ser Glu
          1                               5

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gga ctg caa aca gtg ggt att gtt gtg att ata tgt gca tct ctg aag 339

Gly Leu Gln Thr Val Gly Ile Val Val Ile Ile Cys Ala Ser Leu Lys
 10 15 20 25
 ctg ctt cat ttg ctg gga ctg att gat ttt tcg gaa gac agc gtg gaa 387
 Leu Leu His Leu Leu Gly Leu Ile Asp Phe Ser Glu Asp Ser Val Glu 40
 30 35 40
 gat gaa ctg gag atg gcc act gtc agg cat cgg cct gag gcc ctt gag 435
 Asp Glu Leu Glu Met Ala Thr Val Arg His Arg Pro Glu Ala Leu Glu 55
 45 50 55
 ctt ctg gaa gcc cag agc aaa ttt acc aag aaa gag ctt cag atc ctt 483
 Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu 70
 60 65 70
 tac aga gga ttt aag aac gaa tgc ccc agt ggt gtt gtt aat gaa gaa 531
 Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu 85
 75 80 85
 acc ttc aaa gag att tac tcg cag ttc ttt cca cag gga gac tct aca 579
 Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr 105
 90 95 100 105
 aca tat gca cat ttt ctg ttc aat gcg ttt gat acg gac cac aat gga 627
 Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Thr Asp His Asn Gly 120
 110 115 120
 gct gtg agt ttc gag gat ttc atc aaa ggt ctt tcc att ttg ctc cgg 675
 Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg 135
 125 130 135
 ggg aca gta caa gaa aaa ctc aat tgg gca ttt aat ctg tat gat ata 723
 Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile 150
 140 145 150
 aat aaa gat ggc tac atc act aaa gag gaa atg ctt gat ata atg aaa 771
 Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys 165
 155 160 165
 gca ata tac gac atg atg ggt aaa tgt aca tat cct gtc ctc aaa gaa 819
 Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu 185
 170 175 180 185
 gat gca ccc aga caa cac gtc gaa aca ttt ttt cag aaa atg gac aaa 867
 Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe Gln Lys Met Asp Lys 200
 190 195 200
 aat aaa gat ggg gtt gtt acc ata gat gag ttc att gaa agc tgc caa 915
 Asn Lys Asp Gly Val Val Thr Ile Asp Glu Phe Ile Glu Ser Cys Gln 215
 205 210 215
 aaa gat gaa aac ata atg cgc tcc atg cag ctc ttt gaa aat gtg att 963
 Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Glu Asn Val Ile 230
 220 225 230
 taacttgatca actagatcct gaatccaaca gacaaatgtg aactattcta ccacccttaa 1023
 agtcggagct accactttta gcatagattg ctcagcttga cactgaagca tattatgcaa 1083

- 60 -

acaagctttg ttttaatatata aagcaatccc caaaagattt gagttttctca gttataaatt 1143
 tgcacccctt ccataatgcc actgagttca tgggatgttc taactcattt catactctgt 1203
 gaatattcaa aagtaataga atctggcata tagttttatt gattcccttag ccattgggatt 1263
 attgaggctt tcacatatca gtgattttta aataaccagt ttttttgcgc tcatttgtat 1323
 gtattcagtc ctaggatttt gaatggtttt ctaatatact gacatctgca ttttaatttcc 1383
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 aatcctaaca gcattaaagg ccaaatctgt cctctttccc ctgacttcc taccagcatgt 1863
 ttatattaca agccattcag ggacaaagaa accttgacta cccactgtc tactaggaac 1923
 aaacaaacag caagcaaaat tcactttgaa agcaccagtg gttccattac attgacaact 1983
 actaccaaga ttcagtagaa aataagtgt caacaactaa tccagattac aatatgattt 2043
 agtgcacatc aaaattccaa caattcagat tttttttaat catctcagcc acaactgtaa 2103
 agttgccaca ttactaaaga cacacacatc gtccctgttt ttagaataa tcacaaagac 2163
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 ttctggtgta gagataggat gttgaaagct gccctgctat caccagtgt gaaattaaga 2283
 gtagtacaat acatgtacac tgaaatttgc catcgogtgt ttgtgtaaac tcaatgtgca 2343
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 aaaaaaaaaa 2413

<210> 49
 <211> 233
 <212> PRT
 <213> Simian sp.

<400> 49
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Val Val Ile Ile Cys Ala Ser Leu Lys Leu Leu His Leu Leu Gly Leu
 20 25 30

[illegible]

<210> 50

<211> 1591

<212> DNA

<213> Simian sp.

$\langle 220 \rangle$

<221> CDS

 $\langle 222 \rangle \quad (265) \dots (963)$

<400> 50

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ctttgcaggg tgcagctgcg aggaactgct cacttttttc cccttgcaag tctttgttcc 180
aagcctgacg ttgctacgat tctgtaatta actccctcca ctccaaaggg gtctggaggc 240

tgggatgctc tgccagctca gagg atg ttg act ctg gag tgg gag tcc gaa	291
Met Leu Thr Leu Glu Trp Glu Ser Glu	
1 5	
gga ctg caa aca gtg ggt att gtt gtg att ata tgt gca tct ctg aag	339
Gly Leu Gln Thr Val Gly Ile Val Val Ile Ile Cys Ala Ser Leu Lys	
10 15 20 25	
ctg ctt cat ttg ctg gga ctg att gat ttt tcg gaa gac agc gtg gaa	387
Leu Leu His Leu Leu Gly Leu Ile Asp Phe Ser Glu Asp Ser Val Glu	
30 35 40	
gat gaa ctg gag atg gcc act gtc agg cat cgg cct gag gcc ctt gag	435
Asp Glu Leu Glu Met Ala Thr Val Arg His Arg Pro Glu Ala Leu Glu	
45 50 55	
ctt ctg gaa gcc cag agc aaa ttt acc aag aaa gag ctt cag atc ctt	483
Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu	
60 65 70	
tac aga gga ttt aag aac gaa tgc ccc agt ggt gtt gtt aat gaa gaa	531
Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu	
75 80 85	
acc ttc aaa gag att tac tcg cag ttc ttt cca cag gga gac tct aca	579
Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr	
90 95 100 105	
aca tat gca cat ttt ctg ttc aat gcg ttt gat acg gac cac aat gga	627
Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Thr Asp His Asn Gly	
110 115 120	
gct gtg agt ttc gag gat ttc atc aaa ggt ctt tcc att ttg ctc cgg	675
Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg	
125 130 135	
ggg aca gta caa gaa aaa ctc aat tgg gca ttt aat ctg tat gat ata	723
Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile	
140 145 150	
aat aaa gat ggc tac atc act aaa gag gaa atg ctt gat ata atg aaa	771
Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys	
155 160 165	
gca ata tac gac atg atg ggt aaa tgt aca tat cct gtc ctc aaa gaa	819
Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu	
170 175 180 185	
gat gca ccc aga caa cac gtc gaa aca ttt ttt cag gct gtt ttc cat	867
Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe Gln Ala Val Phe His	
190 195 200	
tgt atc atc aag tgg aag ttc aag acg gca tca aac aaa aca agg atg	915
Cys Ile Ile Lys Trp Lys Phe Lys Thr Ala Ser Asn Lys Thr Arg Met	
205 210 215	
ttt aca gac ata tgc aaa ggg tca gga tat cta tcc tcc agt ata tgt	963
Phe Thr Asp Ile Cys Lys Gly Ser Gly Tyr Leu Ser Ser Ser Ile Cys	
220 225 230	

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taatgcttaa taacaagtaa tcctaacagc attaaaggcc aaatctgtcc tctttccctt 1023
 gatttcctta cagcatgttt atattacaag ccattcaggg acaaagaaac cttgactacc 1083
 ccactgtcta ctaggaacaa acaaacagca agcaaaattc actttgaaag caccagtggg 1143
 tccattacat tgacaactac taccaagatt cagtagaaaa taagtgtca acaactaatc 1203
 cagattacaa tatgatttag tgcatacataa aattccaaca attcagatta tttttaatca 1263
 tctcagccac aactgtaaag ttgccacatt actaaagaca cacacatcgt ccctgttttg 1323
 tagaaatatc acaaagacca agaggctaca gaaggaggaa atttgcaact gtctttgcaa 1383
 caataaatca ggtatctatt ctggtgtaga gataggatgt tgaaagctgc cctgctatca 1443
 ccagtgtaga aattaagagt agtacaatac atgtacactg aaatttgcca tcgctgtgtt 1503
 gtgtaaaactc aatgtgcaca ttttgtatit caaaaagaaa aaataaaaagc aaaataaaat 1563
 gttwawaamw mwaaaaaaaa aaaaaaaaa 1591

<210> 51
 <211> 233
 <212> PRT
 <213> Simian sp.

<400> 51

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Val	Val	Ile	Ile	Cys	Ala	Ser	Leu	Lys	Leu	Leu	His	Leu	Leu	Gly	Leu
			20					25						30	
Ile	Asp	Phe	Ser	Glu	Asp	Ser	Val	Glu	Asp	Glu	Leu	Glu	Met	Ala	Thr
		35					40					45			
Val	Arg	His	Arg	Pro	Glu	Ala	Leu	Glu	Leu	Leu	Glu	Ala	Gln	Ser	Lys
	50					55					60				
Phe	Thr	Lys	Lys	Glu	Leu	Gln	Ile	Leu	Tyr	Arg	Gly	Phe	Lys	Asn	Glu
65					70					75					80
Cys	Pro	Ser	Gly	Val	Val	Asn	Glu	Glu	Thr	Phe	Lys	Glu	Ile	Tyr	Ser
				85					90					95	
Gln	Phe	Phe	Pro	Gln	Gly	Asp	Ser	Thr	Thr	Tyr	Ala	His	Phe	Leu	Phe
			100					105					110		
Asn	Ala	Phe	Asp	Thr	Asp	His	Asn	Gly	Ala	Val	Ser	Phe	Glu	Asp	Phe
	115						120					125			
Ile	Lys	Gly	Leu	Ser	Ile	Leu	Leu	Arg	Gly	Thr	Val	Gln	Glu	Lys	Leu
130						135					140				
Asn	Trp	Ala	Phe	Asn	Leu	Tyr	Asp	Ile	Asn	Lys	Asp	Gly	Tyr	Ile	Thr
145					150					155					160

Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly
 165 170 175

Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val
 180 185 190

Glu Thr Phe Phe Gln Ala Val Phe His Cys Ile Ile Lys Trp Lys Phe
 195 200 205

Lys Thr Ala Ser Asn Lys Thr Arg Met Phe Thr Asp Ile Cys Lys Gly
 210 215 220

Ser Gly Tyr Leu Ser Ser Ser Ile Cys
 225 230

<210> 52

<211> 2051

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (85)..(1305)

<400> 52

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 Met Asn Gly Val Glu Gly Asn Asn Glu
 1 5

ctc cct ctc gct aac acc tcg acc tcc gcc ctt gtc ccg gaa gat ctg 159
 Leu Pro Leu Ala Asn Thr Ser Thr Ser Ala Leu Val Pro Glu Asp Leu
 10 15 20 25

gat ctg aag caa gac cag ccg ctc agc gag gaa act gac acg gtg cgg 207
 Asp Leu Lys Gln Asp Gln Pro Leu Ser Glu Glu Thr Asp Thr Val Arg
 30 35 40

gag atg gag gct gca ggt gag gcc ggt gcg gag gga ggc gcg tcc ccc 255
 Glu Met Glu Ala Ala Gly Glu Ala Gly Ala Glu Gly Gly Ala Ser Pro
 45 50 55

gat tcg gag cac tgc gac ccc cag ctc tgc ctc cga gtg gct gag aat 303
 Asp Ser Glu His Cys Asp Pro Gln Leu Cys Leu Arg Val Ala Glu Asn
 60 65 70

ggc tgt gct gcc gca gcg gga gag ggg ctg gag gat ggt ctg tct tca 351
 Gly Cys Ala Ala Ala Ala Gly Glu Gly Leu Glu Asp Gly Leu Ser Ser
 75 80 85

tca aag tgt ggg gac gca ccc ttg gcg tct gtg gca gcc aac gac agc 399
 Ser Lys Cys Gly Asp Ala Pro Leu Ala Ser Val Ala Ala Asn Asp Ser
 90 95 100 105

aat aaa aat ggc tgt cag ctt gca ggg ccg ctc agc cct gct aag cca 447
 Asn Lys Asn Gly Cys Gln Leu Ala Gly Pro Leu Ser Pro Ala Lys Pro

			110					115					120					
aaa	act	ctg	gaa	gcc	agt	ggt	gca	gtg	ggc	ctg	ggg	tcg	cag	atg	atg	495		
Lys	Thr	Leu	Glu	Ala	Ser	Gly	Ala	Val	Gly	Leu	Gly	Ser	Gln	Met	Met			
			125					130					135					
cca	ggg	ccg	aag	aag	acc	aag	gta	atg	act	acc	aag	ggc	gcc	atc	tct	543		
Pro	Gly	Pro	Lys	Lys	Thr	Lys	Val	Met	Thr	Thr	Lys	Gly	Ala	Ile	Ser			
			140					145					150					
gcg	act	aca	ggc	aag	gaa	gga	gaa	gca	ggg	gcg	gca	atg	cag	gaa	aag	591		
Ala	Thr	Thr	Gly	Lys	Glu	Gly	Glu	Ala	Gly	Ala	Ala	Met	Gln	Glu	Lys			
			155					160					165					
aag	ggg	gtg	cag	aaa	gaa	aaa	aag	gca	gct	gga	gga	ggg	aaa	gac	gag	639		
Lys	Gly	Val	Gln	Lys	Glu	Lys	Lys	Ala	Ala	Gly	Gly	Gly	Lys	Asp	Glu			
			170					175					180					
act	cgt	cct	aga	gcc	cct	aag	atc	aat	aac	tgc	atg	gac	tcc	ctg	gaa	687		
Thr	Arg	Pro	Arg	Ala	Pro	Lys	Ile	Asn	Asn	Cys	Met	Asp	Ser	Leu	Glu			
			190					195					200					
gcc	atc	gat	caa	gag	ctg	tca	aat	gta	aat	gcg	caa	gct	gac	agg	gcc	735		
Ala	Ile	Asp	Gln	Glu	Leu	Ser	Asn	Val	Asn	Ala	Gln	Ala	Asp	Arg	Ala			
			205					210					215					
ttc	ctc	cag	ctg	gaa	cgc	aaa	ttt	ggg	cgg	atg	aga	agg	ctc	cac	atg	783		
Phe	Leu	Gln	Leu	Glu	Arg	Lys	Phe	Gly	Arg	Met	Arg	Arg	Leu	His	Met			
			220					225					230					
cag	cgc	cga	agt	ttc	atc	atc	caa	aac	atc	cca	ggt	ttc	tgg	gtc	aca	831		
Gln	Arg	Arg	Ser	Phe	Ile	Ile	Gln	Asn	Ile	Pro	Gly	Phe	Trp	Val	Thr			
			235					240					245					
gcg	ttt	cgg	aac	cac	ccg	caa	ctg	tca	ccg	atg	atc	agt	ggc	caa	gat	879		
Ala	Phe	Arg	Asn	His	Pro	Gln	Leu	Ser	Pro	Met	Ile	Ser	Gly	Gln	Asp			
			250					255					260					
gaa	gac	atg	atg	agg	tac	atg	atc	aat	tta	gag	gtg	gag	gag	ctt	aag	927		
Glu	Asp	Met	Met	Arg	Tyr	Met	Ile	Asn	Leu	Glu	Val	Glu	Glu	Leu	Lys			
			270					275					280					
cac	cca	aga	gca	ggg	tgc	aaa	ttt	aag	ttc	atc	ttc	caa	agc	aac	ccc	975		
His	Pro	Arg	Ala	Gly	Cys	Lys	Phe	Lys	Phe	Ile	Phe	Gln	Ser	Asn	Pro			
			285					290					295					
tac	ttc	cga	aat	gag	ggg	ctg	gtc	aaa	gag	tac	gag	cgc	aga	tcc	tca	1023		
Tyr	Phe	Arg	Asn	Glu	Gly	Leu	Val	Lys	Glu	Tyr	Glu	Arg	Arg	Ser	Ser			
			300					305					310					
ggt	cga	gtg	gtg	tcg	ctc	tct	acg	cca	atc	cgc	tgg	cac	cgg	ggt	caa	1071		
Gly	Arg	Val	Val	Ser	Leu	Ser	Thr	Pro	Ile	Arg	Trp	His	Arg	Gly	Gln			
			315					320					325					
gaa	ccc	cag	gcc	cat	atc	cac	agg	aat	aga	gag	ggg	aac	acg	att	ccc	1119		
Glu	Pro	Gln	Ala	His	Ile	His	Arg	Asn	Arg	Glu	Gly	Asn	Thr	Ile	Pro			
			330					335					340					
agt	ttc	ttc	aat	tgg	ttc	tca	gac	cac										

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Ser Phe Phe Asn Trp Phe Ser Asp His Ser Leu Leu Glu Phe Asp Arg
 350 355 360
 ata gct gaa att atc aaa ggg gag ctt tgg tcc aat ccc cta caa tac 1215
 Ile Ala Glu Ile Ile Lys Gly Glu Leu Trp Ser Asn Pro Leu Gln Tyr
 365 370 375
 tac ctg atg ggc gat ggg cca cgc aga gga gtt cga gtc cca cca agg 1263
 Tyr Leu Met Gly Asp Gly Pro Arg Arg Gly Val Arg Val Pro Pro Arg
 380 385 390
 cag cca gtg gag agt ccc agg tcc ttc agg ttc cag tct ggc 1305
 Gln Pro Val Glu Ser Pro Arg Ser Phe Arg Phe Gln Ser Gly
 395 400 405
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 gaagtattag gtgaggagtg ttttctgtca ccacattgtt cttgtaccaa tgcacatga 1965
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<210> 53
 <211> 407
 <212> PRT
 <213> Rattus sp.

<400> 53
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 Thr Ser Ala Leu Val Pro Glu Asp Leu Asp Leu Lys Gln Asp Gln Pro
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 Leu Ser Glu Glu Thr Asp Thr Val Arg Glu Met Glu Ala Ala Gly Glu
 35 40 45
 Ala Gly Ala Glu Gly Gly Ala Ser Pro Asp Ser Glu His Cys Asp Pro

Gln	Leu	Cys	Leu	Arg	Val	Ala	Glu	Asn	Gly	Cys	Ala	Ala	Ala	Ala	Ala	Gly	
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Glu	Gly	Leu	Glu	Asp	Gly	Leu	Ser	Ser	Ser	Lys	Cys	Gly	Asp	Ala	Pro		
				85					90					95			
Leu	Ala	Ser	Val	Ala	Ala	Asn	Asp	Ser	Asn	Lys	Asn	Gly	Cys	Gln	Leu		
			100					105					110				
Ala	Gly	Pro	Leu	Ser	Pro	Ala	Lys	Pro	Lys	Thr	Leu	Glu	Ala	Ser	Gly		
		115					120					125					
Ala	Val	Gly	Leu	Gly	Ser	Gln	Met	Met	Pro	Gly	Pro	Lys	Lys	Thr	Lys		
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Val	Met	Thr	Thr	Lys	Gly	Ala	Ile	Ser	Ala	Thr	Thr	Gly	Lys	Glu	Gly		
145					150					155					160		
Glu	Ala	Gly	Ala	Ala	Met	Gln	Glu	Lys	Lys	Gly	Val	Gln	Lys	Glu	Lys		
				165					170					175			
Lys	Ala	Ala	Gly	Gly	Gly	Lys	Asp	Glu	Thr	Arg	Pro	Arg	Ala	Pro	Lys		
			180					185					190				
Ile	Asn	Asn	Cys	Met	Asp	Ser	Leu	Glu	Ala	Ile	Asp	Gln	Glu	Leu	Ser		
		195					200					205					
Asn	Val	Asn	Ala	Gln	Ala	Asp	Arg	Ala	Phe	Leu	Gln	Leu	Glu	Arg	Lys		
	210					215					220						
Phe	Gly	Arg	Met	Arg	Arg	Leu	His	Met	Gln	Arg	Arg	Ser	Phe	Ile	Ile		
225					230					235					240		
Gln	Asn	Ile	Pro	Gly	Phe	Trp	Val	Thr	Ala	Phe	Arg	Asn	His	Pro	Gln		
				245					250					255			
Leu	Ser	Pro	Met	Ile	Ser	Gly	Gln	Asp	Glu	Asp	Met	Met	Arg	Tyr	Met		
			260					265					270				
Ile	Asn	Leu	Glu	Val	Glu	Glu	Leu	Lys	His	Pro	Arg	Ala	Gly	Cys	Lys		
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Phe	Lys	Phe	Ile	Phe	Gln	Ser	Asn	Pro	Tyr	Phe	Arg	Asn	Glu	Gly	Leu		
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Val	Lys	Glu	Tyr	Glu	Arg	Arg	Ser	Ser	Gly	Arg	Val	Val	Ser	Leu	Ser		
305					310					315					320		
Thr	Pro	Ile	Arg	Trp	His	Arg	Gly	Gln	Glu	Pro	Gln	Ala	His	Ile	His		
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Arg	Asn	Arg	Glu	Gly	Asn	Thr	Ile	Pro	Ser	Phe	Phe	Asn	Trp	Phe	Ser		
			340					345					350				
Asp	His	Ser	Leu	Leu	Glu	Phe	Asp	Arg	Ile	Ala	Glu	Ile	Ile	Lys	Gly		
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Glu Leu Trp Ser Asn Pro Leu Gln Tyr Tyr Leu Met Gly Asp Gly Pro
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Arg Arg Gly Val Arg Val Pro Pro Arg Gln Pro Val Glu Ser Pro Arg
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Ser Phe Arg Phe Gln Ser Gly
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 <213> Homo sapiens

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 <222> (88)..(1329)

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 Met Ser Gly Leu Asp Gly Gly Asn Lys
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ctc cct ctc gcc caa acc ggc ggc ctg gct gct ccc gac cat gcc tca 162
 Leu Pro Leu Ala Gln Thr Gly Gly Leu Ala Ala Pro Asp His Ala Ser
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gga gat ccg gac cta gac cag tgc caa ggg ctc cgt gaa gaa acc gag 210
 Gly Asp Pro Asp Leu Asp Gln Cys Gln Gly Leu Arg Glu Glu Thr Glu
 30 35 40

gcg aca cag gtg atg gcg aac aca ggt ggg ggc agc ctg gag acc gtt 258
 Ala Thr Gln Val Met Ala Asn Thr Gly Gly Gly Ser Leu Glu Thr Val
 45 50 55

gcg gag ggg ggt gca tcc cag gat cct gtc gac tgt ggc ccc gcg ctc 306
 Ala Glu Gly Gly Ala Ser Gln Asp Pro Val Asp Cys Gly Pro Ala Leu
 60 65 70

cgc gtc cca gtt gcc ggg agt cgc ggc ggt gca gcg acc aaa gcc ggg 354
 Arg Val Pro Val Ala Gly Ser Arg Gly Gly Ala Ala Thr Lys Ala Gly
 75 80 85

cag gag gat gct cca cct tct acg aaa ggt ctg gaa gca gcc tct gcc 402
 Gln Glu Asp Ala Pro Pro Ser Thr Lys Gly Leu Glu Ala Ala Ser Ala
 90 95 100 105

gcc gag gct gct gac agc agc cag aaa aat ggc tgt cag ctt gga gag 450
 Ala Glu Ala Ala Asp Ser Ser Gln Lys Asn Gly Cys Gln Leu Gly Glu
 110 115 120

ccc cgt ggc cct gct ggg cag aag gct cta gaa gcc tgt ggc gca ggg 498
 Pro Arg Gly Pro Ala Gly Gln Lys Ala Leu Glu Ala Cys Gly Ala Gly
 125 130 135

ggc ttg ggg tct cag atg ata ccg ggg aag aag gcc aag gaa gtg acg 546

Gly Leu Gly Ser Gln Met Ile Pro Gly Lys Lys Ala Lys Glu Val Thr	
140 145 150	
act aaa aaa cgc gcc atc tcg gca gca gtg gaa aag gag gga gaa gca	594
Thr Lys Lys Arg Ala Ile Ser Ala Ala Val Glu Lys Glu Gly Glu Ala	
155 160 165	
ggg gcg gcg atg gag gaa aag aag gta gtg cag aag gaa aaa aag gtg	642
Gly Ala Ala Met Glu Glu Lys Lys Val Val Gln Lys Glu Lys Lys Val	
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gca gga ggg gtg aaa gag gag aca cgg ccc agg gcc ccg aag atc aat	690
Ala Gly Gly Val Lys Glu Glu Thr Arg Pro Arg Ala Pro Lys Ile Asn	
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aac tgc atg gac tca ctg gag gcc atc gat caa gag ttg tca aac gta	738
Asn Cys Met Asp Ser Leu Glu Ala Ile Asp Gln Glu Leu Ser Asn Val	
205 210 215	
aat gcc cag gct gac agg gcc ttc ctt cag ctt gag cgc aag ttt ggc	786
Asn Ala Gln Ala Asp Arg Ala Phe Leu Gln Leu Glu Arg Lys Phe Gly	
220 225 230	
cgc atg cga agg ctc cac atg cag cgc aga agt ttc att atc cag aat	834
Arg Met Arg Arg Leu His Met Gln Arg Arg Ser Phe Ile Ile Gln Asn	
235 240 245	
atc cca ggt ttc tgg gtt act gcc ttt cga aac cac ccc cag ctg tca	882
Ile Pro Gly Phe Trp Val Thr Ala Phe Arg Asn His Pro Gln Leu Ser	
250 255 260 265	
cct atg atc agt ggc caa gat gaa gac atg ctg agg tac atg atc aat	930
Pro Met Ile Ser Gly Gln Asp Glu Asp Met Leu Arg Tyr Met Ile Asn	
270 275 280	
ttg gag gtg gag gag ctt aaa cac ccc aga gca ggc tgc aaa ttc aag	978
Leu Glu Val Glu Glu Leu Lys His Pro Arg Ala Gly Cys Lys Phe Lys	
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ttc atc ttt cag ggc aac ccc tac ttc cga aat gag ggg ctt gtc aag	1026
Phe Ile Phe Gln Gly Asn Pro Tyr Phe Arg Asn Glu Gly Leu Val Lys	
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gaa tat gaa cgc aga tcc tct ggc cgg gtg gtg tct ctt tcc act cca	1074
Glu Tyr Glu Arg Arg Ser Ser Gly Arg Val Val Ser Leu Ser Thr Pro	
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Ile Arg Trp His Arg Gly Gln Asp Pro Gln Ala His Ile His Arg Asn	
330 335 340 345	
cgg gaa ggg aac act atc cct agt ttc ttc aac tgg ttt tca gac cac	1170
Arg Glu Gly Asn Thr Ile Pro Ser Phe Phe Asn Trp Phe Ser Asp His	
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agc ctt cta gaa ttc gac aga att gca gag att atc aaa gga gaa ctg	1218
Ser Leu Leu Glu Phe Asp Arg Ile Ala Glu Ile Ile Lys Gly Glu Leu	
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tgg ccc aat ccc cta caa tac tac ctg atg ggt gaa ggg ccc cgt aga 1266
 Trp Pro Asn Pro Leu Gln Tyr Tyr Leu Met Gly Glu Gly Pro Arg Arg
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gga att cga ggc cca cca agg cag cca gtg gag agc gcc aga tcc ttc 1314
 Gly Ile Arg Gly Pro Pro Arg Gln Pro Val Glu Ser Ala Arg Ser Phe
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agg ttc cag tct ggc taatctctgt cctgtgagaa gcttctgcac aagtttcctt 1369
 Arg Phe Gln Ser Gly
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<211> 414

<212> PRT

<213> Homo sapiens

<400> 55

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			20					25						30	

Cys Gln Gly Leu Arg Glu Glu Thr Glu Ala Thr Gln Val Met Ala Asn
 35 40 45
 Thr Gly Gly Gly Ser Leu Glu Thr Val Ala Glu Gly Gly Ala Ser Gln
 50 55 60
 Asp Pro Val Asp Cys Gly Pro Ala Leu Arg Val Pro Val Ala Gly Ser
 65 70 75 80
 Arg Gly Gly Ala Ala Thr Lys Ala Gly Gln Glu Asp Ala Pro Pro Ser
 85 90 95
 Thr Lys Gly Leu Glu Ala Ala Ser Ala Ala Glu Ala Ala Asp Ser Ser
 100 105 110
 Gln Lys Asn Gly Cys Gln Leu Gly Glu Pro Arg Gly Pro Ala Gly Gln
 115 120 125
 Lys Ala Leu Glu Ala Cys Gly Ala Gly Gly Leu Gly Ser Gln Met Ile
 130 135 140
 Pro Gly Lys Lys Ala Lys Glu Val Thr Thr Lys Lys Arg Ala Ile Ser
 145 150 155 160
 Ala Ala Val Glu Lys Glu Gly Glu Ala Gly Ala Ala Met Glu Glu Lys
 165 170 175
 Lys Val Val Gln Lys Glu Lys Lys Val Ala Gly Gly Val Lys Glu Glu
 180 185 190
 Thr Arg Pro Arg Ala Pro Lys Ile Asn Asn Cys Met Asp Ser Leu Glu
 195 200 205
 Ala Ile Asp Gln Glu Leu Ser Asn Val Asn Ala Gln Ala Asp Arg Ala
 210 215 220
 Phe Leu Gln Leu Glu Arg Lys Phe Gly Arg Met Arg Arg Leu His Met
 225 230 235 240
 Gln Arg Arg Ser Phe Ile Ile Gln Asn Ile Pro Gly Phe Trp Val Thr
 245 250 255
 Ala Phe Arg Asn His Pro Gln Leu Ser Pro Met Ile Ser Gly Gln Asp
 260 265 270
 Glu Asp Met Leu Arg Tyr Met Ile Asn Leu Glu Val Glu Glu Leu Lys
 275 280 285
 His Pro Arg Ala Gly Cys Lys Phe Lys Phe Ile Phe Gln Gly Asn Pro
 290 295 300
 Tyr Phe Arg Asn Glu Gly Leu Val Lys Glu Tyr Glu Arg Arg Ser Ser
 305 310 315 320
 Gly Arg Val Val Ser Leu Ser Thr Pro Ile Arg Trp His Arg Gly Gln
 325 330 335

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Asp Pro Gln Ala His Ile His Arg Asn Arg Glu Gly Asn Thr Ile Pro
 340 345 350

Ser Phe Phe Asn Trp Phe Ser Asp His Ser Leu Leu Glu Phe Asp Arg
 355 360 365

Ile Ala Glu Ile Ile Lys Gly Glu Leu Trp Pro Asn Pro Leu Gln Tyr
 370 375 380

Tyr Leu Met Gly Glu Gly Pro Arg Arg Gly Ile Arg Gly Pro Pro Arg
 385 390 395 400

Gln Pro Val Glu Ser Ala Arg Ser Phe Arg Phe Gln Ser Gly
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<210> 56

<211> 2643

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1)..(801)

<400> 56

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aac cat ggc tca gct ctg cac atc gct gcc tcg aat ctg tgc ctg ggc	96
Asn His Gly Ser Ala Leu His Ile Ala Ala Ser Asn Leu Cys Leu Gly	
20 25 30	
gcc gcc aaa tgt tta ctg gag cat ggt gcc aac cca gcg ctg agg aat	144
Ala Ala Lys Cys Leu Leu Glu His Gly Ala Asn Pro Ala Leu Arg Asn	
35 40 45	
cga aaa gga cag gta cca gcg gaa gtg gtc cca gac ccc atg gac atg	192
Arg Lys Gly Gln Val Pro Ala Glu Val Val Pro Asp Pro Met Asp Met	
50 55 60	
tcc ctt gac aag gca gag gca gcc ctg gtg gcc aag gaa ttg cgg acg	240
Ser Leu Asp Lys Ala Glu Ala Ala Leu Val Ala Lys Glu Leu Arg Thr	
65 70 75 80	
ctg cta gaa gag gct gtg cca ctg tcc tgc acc ctt cct aaa gtc aca	288
Leu Leu Glu Glu Ala Val Pro Leu Ser Cys Thr Leu Pro Lys Val Thr	
85 90 95	
cta ccc aac tat gac aac gtc cca ggc aat ctc atg ctc agc gcg ctg	336
Leu Pro Asn Tyr Asp Asn Val Pro Gly Asn Leu Met Leu Ser Ala Leu	
100 105 110	
ggc ctg cgt cta gga gac cga gtg ctc ctc gat ggc cag aag acg ggc	384
Gly Leu Arg Leu Gly Asp Arg Val Leu Leu Asp Gly Gln Lys Thr Gly	
115 120 125	
acg ctg agg ttc tgc ggg acc acc gag ttc gcc agt ggc cag tgg gtg	432

Thr Leu Arg Phe Cys Gly Thr Thr Glu Phe Ala Ser Gly Gln Trp Val
 130 135 140
 ggc gtg gag cta gat gaa ccg gaa ggc aag aac gac ggc agc gtt ggg 480
 Gly Val Glu Leu Asp Glu Pro Glu Gly Lys Asn Asp Gly Ser Val Gly
 145 150 155 160
 ggt gtc cgg tac ttc atc tgc cct ccc aag cag ggt ctc ttt gca tct 528
 Gly Val Arg Tyr Phe Ile Cys Pro Pro Lys Gln Gly Leu Phe Ala Ser
 165 170 175
 gtg tcc aag gtc tcc aag gca gtg gat gca ccc ccc tca tct gtt acc 576
 Val Ser Lys Val Ser Lys Ala Val Asp Ala Pro Pro Ser Ser Val Thr
 180 185 190
 tcc acg ccc cgc act ccc cgg atg gac ttc tcc cgt gta acg ggc aaa 624
 Ser Thr Pro Arg Thr Pro Arg Met Asp Phe Ser Arg Val Thr Gly Lys
 195 200 205
 ggc cgg agg gaa cac aaa ggg aag aag aag tcc cca tct tcc cca tct 672
 Gly Arg Arg Glu His Lys Gly Lys Lys Lys Ser Pro Ser Ser Pro Ser
 210 215 220
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 225 230 235 240
 caa gtc ctt gtg gca ggc cag aac agg gat tgt gcg ttt cta tgg gaa 768
 Gln Val Leu Val Ala Gly Gln Asn Arg Asp Cys Ala Phe Leu Trp Glu
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<210> 57

<211> 267

<212> PRT

<213> Rattus sp.

<400> 57

Leu Lys Gly Ala Arg Pro Arg Val Val Asn Ser Thr Cys Ser Asp Phe
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Asn His Gly Ser Ala Leu His Ile Ala Ala Ser Asn Leu Cys Leu Gly
 20 25 30

Ala Ala Lys Cys Leu Leu Glu His Gly Ala Asn Pro Ala Leu Arg Asn
 35 40 45

Arg Lys Gly Gln Val Pro Ala Glu Val Val Pro Asp Pro Met Asp Met
 50 55 60

Ser Leu Asp Lys Ala Glu Ala Ala Leu Val Ala Lys Glu Leu Arg Thr

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gga aac cct gag aga gaa ggg agt gtc agc att gta gga gca gtt tct			192
Gly Asn Pro Glu Arg Glu Gly Ser Val Ser Ile Val Gly Ala Val Ser			
50	55	60	
cca cct ggt ggt gat ttt tct gat cca gtc aca tct gct act ctg ggt			240
Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly			
65	70	75	80
att gtt cag gtg ttc tgg ggc ttg gat aag aag cta gct cag cgc aag			288
Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys			
85	90	95	
cac ttc ccg tcc gtc aac tgg ctc att agc tac agc aag tac atg cgc			336
His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg			
100	105	110	
gcc ctg gac gag tac tat gac aaa cac ttc aca gag ttc gtg cct ctg			384
Ala Leu Asp Glu Tyr Tyr Asp Lys His Phe Thr Glu Phe Val Pro Leu			
115	120	125	
agg acc aaa gct aag gag att ctg cag gaa gag gag gat ctg gcg gaa			432
Arg Thr Lys Ala Lys Glu Ile Leu Gln Glu Glu Glu Asp Leu Ala Glu			
130	135	140	
atc gtg cag ctc gtg gga aag gcg tct tta gca gag aca gat aaa atc			480
Ile Val Gln Leu Val Gly Lys Ala Ser Leu Ala Glu Thr Asp Lys Ile			
145	150	155	160
acc ctg gag gta gca aaa ctt atc aaa gat gac ttc cta caa caa aat			528
Thr Leu Glu Val Ala Lys Leu Ile Lys Asp Asp Phe Leu Gln Gln Asn			
165	170	175	
ggg tac act cct tat gac agg ttc tgt cca ttc tat aag acg gtg ggg			576
Gly Tyr Thr Pro Tyr Asp Arg Phe Cys Pro Phe Tyr Lys Thr Val Gly			
180	185	190	
atg ctg tcc aac atg att tca ttc tat gat atg gcc cgc cgg gct gtg			624
Met Leu Ser Asn Met Ile Ser Phe Tyr Asp Met Ala Arg Arg Ala Val			
195	200	205	
gag acc acc gcc cag agt gac aat aag atc aca tgg tcc att atc cgt			672
Glu Thr Thr Ala Gln Ser Asp Asn Lys Ile Thr Trp Ser Ile Ile Arg			
210	215	220	
gag cac atg ggg gag att ctc tat aaa ctt tcc tcc atg aaa ttc aag			720
Glu His Met Gly Glu Ile Leu Tyr Lys Leu Ser Ser Met Lys Phe Lys			
225	230	235	240
gat cca gtg aag gat ggc gag gca aag atc aag gcc gac tac gca cag			768
Asp Pro Val Lys Asp Gly Glu Ala Lys Ile Lys Ala Asp Tyr Ala Gln			
245	250	255	
ctt ctt gaa gat atg cag aac gca ttc cgt agc ctg gaa gat			810
Leu Leu Glu Asp Met Gln Asn Ala Phe Arg Ser Leu Glu Asp			
260	265	270	
tagaactgtg acttctctcc tctcttccg cagctcatat gtgtatatatt tcttgaattt			870

ctcatctcca accctttgct tccatattgt gcagctttga gactagtgcc tcgtgcgttc 930
tcgttcattt tgctgtttct ttggtaggtc ttataaaaca cacattcctg tgctccgctg 990
tctgaaggag ctctgacct ttgtctgaag tggatgaatgt agtgcataatg atacacagt 1050
taacatacac attgtaacat atacgttctg taaacttgta tgtaaggatga ctaccccttc 1110
cctcctctcc agtaaactgt aaacaggact actgcatgtg ctctattggg gatggaaggc 1170
cagatctcca taccgtggac aggtacataa ggaaactaga ccacttgcaa cttagtgttt 1230
gttgagtaac ctttttgag gaagtatttc cttttaaaaa acaaaagatt aatgttccaa 1290
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gttttcctaa cagacgtttg caaggctgaa cgtaatagat aaatcagttc cctctgaaag 1410
tgtgaaagta aaaagagagc taggtggtca gacttaaatt gacatcgtct tgtttaagca 1470
tattttattt cactgagaga tttaatatca aggactttta tatactcaat tactaggaaa 1530
tcttttttta agtacaattt aaaaatcatt gaaaatgtga tccacatcat agccattttc 1590
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acgcagcagt gcctgcaggc agtgtggccg ggggccagag cggcattgtt ttcacgaggt 1710
acgtgtgtgg cgtgtgtgtt tgcttggtga cactctgaaa acagcaagct taccagttcc 1770
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atttgcataa cgaggctcgc ttctgagagc ttggagatcg tgctccctct tcaactctccg 2010
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acctaggctt gtgatcagaa tgaatgatcc caagaaacta cttgaccaag tgtgttttgt 2490
tgtcctggat ttgagatgtg cgttcttctc cctctgaga ctgttgatgt atgagtgtga 2550
agaagttaca gaaacaacgc tcagattttc acggtaactt tccctctgcc cacactgtag 2610

agtttcagat tgttccactga tagtgcttct ttcgtaagga tgtgttaaaa tatagcagtc 2670
 tttttaaaag attatgcagt tctctattta ttgtgctgtg cctggctcta agtgcagccg 2730
 gttaaacaag tttcatatgt atttttccag tgttaaattct catacctatg ccctttggaa 2790
 agctccatcc tgaacaatga atagaagagg ctatataaat tgcctcctta tccttaagat 2850
 ttcactatct ttatgttaag agtaatgtat aattattaaa atctatgaaa aataaaaaagt 2910
 ggattttaa at taagagatc 2929

<210> 59

<211> 270

<212> PRT

<213> Rattus sp.

<400> 59

Ala Asp Ser Thr Ser Arg Trp Ala Glu Ala Leu Arg Glu Ile Ser Gly
 1 5 10 15
 Arg Leu Ala Glu Met Pro Ala Asp Ser Gly Tyr Pro Ala Tyr Leu Gly
 20 25 30
 Ala Arg Leu Ala Ser Phe Tyr Glu Arg Ala Gly Arg Val Lys Cys Leu
 35 40 45
 Gly Asn Pro Glu Arg Glu Gly Ser Val Ser Ile Val Gly Ala Val Ser
 50 55 60
 Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly
 65 70 75 80
 Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys
 85 90 95
 His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg
 100 105 110
 Ala Leu Asp Glu Tyr Tyr Asp Lys His Phe Thr Glu Phe Val Pro Leu
 115 120 125
 Arg Thr Lys Ala Lys Glu Ile Leu Gln Glu Glu Asp Leu Ala Glu
 130 135 140
 Ile Val Gln Leu Val Gly Lys Ala Ser Leu Ala Glu Thr Asp Lys Ile
 145 150 155 160
 Thr Leu Glu Val Ala Lys Leu Ile Lys Asp Asp Phe Leu Gln Gln Asn
 165 170 175
 Gly Tyr Thr Pro Tyr Asp Arg Phe Cys Pro Phe Tyr Lys Thr Val Gly
 180 185 190
 Met Leu Ser Asn Met Ile Ser Phe Tyr Asp Met Ala Arg Arg Ala Val
 195 200 205
 Glu Thr Thr Ala Gln Ser Asp Asn Lys Ile Thr Trp Ser Ile Ile Arg

210 215 220
 Glu His Met Gly Glu Ile Leu Tyr Lys Leu Ser Ser Met Lys Phe Lys
 225 230 235 240
 Asp Pro Val Lys Asp Gly Glu Ala Lys Ile Lys Ala Asp Tyr Ala Gln
 245 250 255
 Leu Leu Glu Asp Met Gln Asn Ala Phe Arg Ser Leu Glu Asp
 260 265 270

 <210> 60
 <211> 1489
 <212> DNA
 <213> Rattus sp.

 <220>
 <221> CDS
 <222> (1)..(1053)

 <400> 60
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 Ala Arg Leu Pro Ala Pro Glu His Ala Arg Gln Gln Pro Leu Leu Ser
 1 5 10 15
 ggc cct gag ccc gga tcg tcc gcc cgg gtt cca gtt ccc ggc gtg gcc 96
 Gly Pro Glu Pro Gly Ser Ser Ala Arg Val Pro Val Pro Gly Val Ala
 20 25 30
 agt agg cgg cag ccg cga ggc ggc aag cca ccc agc ggg gac ggc ctg 144
 Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
 35 40 45

 gag tcg ggc ccc tct cca cgc ccc ctt ctc cac gcg cgc ggg gag gca 192
 Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
 50 55 60
 ggg ctc cac cgc cag tct gga agg gtt cca cat aca gga acg gcc tac 240
 Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
 65 70 75 80
 ttc gca gat gag ccc acc gag gct cag gct ccg ggc gga ttc tgc gtg 288
 Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
 85 90 95
 tca ccc tcg ctc ctt ggg gtc cgc tgg ccg gcc tgt gcc acc cgg acg 336
 Ser Pro Ser Leu Leu Gly Val Arg Trp Pro Ala Cys Ala Thr Arg Thr
 100 105 110
 ccc ggc tca ctg cct ctg tet ccc cca tca gcg cag ccc cgg acg cta 384
 Pro Gly Ser Leu Pro Leu Ser Pro Pro Ser Ala Gln Pro Arg Thr Leu
 115 120 125
 tgg ccc acc cct cca gct ggc ccc tcg agt agg atg gta gca cgt aac 432
 Trp Pro Thr Pro Pro Ala Gly Pro Ser Ser Arg Met Val Ala Arg Asn
 130 135 140

cag gtg gca gcc gac aat gcg atc tcc ccg gca tca gag ccc cga cgg 480
 Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala Ser Glu Pro Arg Arg
 145 150 155 160

cgg cca gag cca tcc tcg tcc tcg tct tcg tcc tcg ccg gcg gcc ccg 528
 Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser Pro Ala Ala Pro
 165 170 175

gcg cgt ccc cgg ccc tgc ccg gtg gtc ccg gcc ccg gct ccg gcc gac 576
 Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala Pro Ala Pro Gly Asp
 180 185 190

act cac ttc cgc acc ttc cgc tcc cac tct gat tac ccg cgc atc acg 624
 Thr His Phe Arg Thr Phe Arg Ser His Ser Asp Tyr Arg Arg Ile Thr
 195 200 205

cgg acc agc gct ctc ctg gac gcc tgc gcc ttc tac tgg gga ccc ctg 672
 Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr Trp Gly Pro Leu
 210 215 220

agc gtg cat ggg gcg cac gaa ccg ctg cgt gcc gag ccc gtg gcc acc 720
 Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu Pro Val Gly Thr
 225 230 235 240

ttc ttg gtg cgc gac agt cgc cag ccg aac tgc ttc ttc gcg ctc agc 768
 Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe Phe Ala Leu Ser
 245 250 255

gtg aag atg gct tcg gcc ccc acg agc att cgt gtg cac ttc cag gcc 816
 Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val His Phe Gln Ala
 260 265 270

gcc cgc ttc cac ctg gac gcc agc cgc gag acc ttc gac tgc ctc ttc 864
 Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr Phe Asp Cys Leu Phe
 275 280 285

gag ctg ctg gag cac tac gtg gcg gcg ccg cgc cgc atg ttg ggg gcc 912
 Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg Met Leu Gly Ala
 290 295 300

cca ctg cgc cag cgc cgc gtg ccg ccg ctg cag gag ctg tgt cgc cag 960
 Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu Leu Cys Arg Gln
 305 310 315 320

cgc atc gtg gcc gcc gtg ggt cgc gag aac ctg gca cgc atc cct ctt 1008
 Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu Ala Arg Ile Pro Leu
 325 330 335

aac ccg gta ctc cgt gac tac ctg agt tcc ttc ccc ttc cag atc 1053
 Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro Phe Gln Ile
 340 345 350

tgaccggctg ccgccgtgcc cgcagcatta agtgggagcg ccttattatt tcttattatt 1113

aattattatt atttttctgg aaccacgtgg gagccctccc cgcctaggtc ggagggagtg 1173

ggtgtggagg gtgagatgcc tcccacttct ggctggagac cttatcccgcc ctctcggggg 1233

gcctccctc ctggtgctcc ctcccggtcc cctggttgt agcagcttgt gtctggggcc 1293
 aggacctgaa ctccacgcct acctctccat gtttacatgt tcccagtatc tttgcacaaa 1353
 ccaggggtgg gggaggggtct ctggcttcat tttctgctg tgcagaatat tctattttat 1413
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 aaaaaaaaaa aaaaaa 1489

<210> 61
 <211> 351
 <212> PRT
 <213> Rattus sp.

<400> 61
 Ala Arg Leu Pro Ala Pro Glu His Ala Arg Gln Gln Pro Leu Leu Ser
 1 5 10 15
 Gly Pro Glu Pro Gly Ser Ser Ala Arg Val Pro Val Pro Gly Val Ala
 20 25 30
 Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
 35 40 45
 Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
 50 55 60
 Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
 65 70 75 80
 Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
 85 90 95
 Ser Pro Ser Leu Leu Gly Val Arg Trp Pro Ala Cys Ala Thr Arg Thr
 100 105 110
 Pro Gly Ser Leu Pro Leu Ser Pro Pro Ser Ala Gln Pro Arg Thr Leu
 115 120 125
 Trp Pro Thr Pro Pro Ala Gly Pro Ser Ser Arg Met Val Ala Arg Asn
 130 135 140
 Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala Ser Glu Pro Arg Arg
 145 150 155 160
 Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser Pro Ala Ala Pro
 165 170 175
 Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala Pro Ala Pro Gly Asp
 180 185 190
 Thr His Phe Arg Thr Phe Arg Ser His Ser Asp Tyr Arg Arg Ile Thr
 195 200 205
 Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr Trp Gly Pro Leu

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210	215	220
Ser Val His Gly Ala	His Glu Arg Leu Arg	Ala Glu Pro Val Gly Thr
225	230	235 240
Phe Leu Val Arg Asp	Ser Arg Gln Arg Asn Cys Phe Phe	Ala Leu Ser
	245	250 255
Val Lys Met Ala Ser Gly Pro Thr	Ser Ile Arg Val His Phe Gln Ala	
	260	265 270
Gly Arg Phe His Leu Asp Gly	Ser Arg Glu Thr Phe Asp Cys Leu Phe	
	275	280 285
Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg	Arg Met Leu Gly Ala	
	290	295 300
Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu Leu Cys Arg Gln		
305	310	315 320
Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu Ala Arg Ile Pro Leu		
	325	330 335
Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro Phe Gln Ile		
	340	345 350

<210> 62
 <211> 1194
 <212> DNA
 <213> Rattus sp.

<220>
 <221> CDS
 <222> (130)..(765)

<400> 62
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 ccccgctcc cgccgccagc gcagccccgg acgctatggc ccacccctcc agctggcccc 120

tcgagtagg atg gta gca cgt aac cag gtg gca gcc gac aat gcg atc tcc 171
 Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser
 1 5 10

ccg gca tca gag ccc cga cgg cgg cca gag cca tcc tcg tcc tcg tct 219
 Pro Ala Ser Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser
 15 20 25 30

tcg tcc tcg ccg gcg gcc ccg gcg cgt ccc cgg ccc tgc ccg gtg gtc 267
 Ser Ser Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val
 35 40 45

ccg gcc ccg gct ccg ggc gac act cac ttc cgc acc ttc cgc tcc cac 315
 Pro Ala Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His
 50 55 60

tct gat tac cgg cgc atc acg cgg acc agc gct ctc ctg gac gcc tgc 363

Ser Asp Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys
 65 70 75
 ggc ttc tac tgg gga ccc ctg agc gtg cat ggg gcg cac gaa cgg ctg 411
 Gly Phe Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu
 80 85 90
 cgt gcc gag ccc gtg ggc acc ttc ttg gtg cgc gac agt cgc cag cgg 459
 Arg Ala Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg
 95 100 105 110
 aac tgc ttc ttc gcg ctc agc gtg aag atg gct tcg ggc ccc acg agc 507
 Asn Cys Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser
 115 120 125
 att cgt gtg cac ttc cag gcc ggc cgc ttc cac ctg gac ggc agc cgc 555
 Ile Arg Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg
 130 135 140
 gag acc ttc gac tgc ctc ttc gag ctg ctg gag cac tac gtg gcg gcg 603
 Glu Thr Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala
 145 150 155
 ccg cgc cgc atg ttg ggg gcc cca ctg cgc cag cgc cgc gtg cgg ccg 651
 Pro Arg Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro
 160 165 170
 ctg cag gag ctg tgt cgc cag cgc atc gtg gcc gcc gtg ggt cgc gag 699
 Leu Gln Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu
 175 180 185 190
 aac ctg gca cgc atc cct ctt aac ccg gta ctc cgt gac tac ctg agt 747
 Asn Leu Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser
 195 200 205
 tcc ttc ccc ttc cag atc tgaccggctg ccgccgtgcc cgcagcatta 795
 Ser Phe Pro Phe Gln Ile
 210
 agtgggagcg ccttattatt tcttattatt aattattatt atttttctgg aaccacgtgg 855
 gageccctccc cgcctaggtc ggagggagtg ggtgtggagg gtgagatgcc tcccacttct 915
 ggctggagac cttatccgc ctctcggggg gcctcccctc ctggtgctcc ctcccgggtcc 975
 ccctggttgt agcagcttgt gtctggggcc aggacctgaa ctccacgcct acctctccat 1035
 gtttacatgt tccagtatc ttgcacaaa ccaggggttg gggagggctc ctggcttcat 1095
 tttctgctg tgcagaatat tctattttat atttttacat ccagtttaga taataaactt 1155
 tattatgaaa gttttttttt taaaaaaaaa aaaaaaaaaa 1194

<210> 63
 <211> 212
 <212> PRT
 <213> Rattus sp.

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<400> 63

Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala
 1 5 10 15

Ser Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser
 20 25 30

Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala
 35 40 45

Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ser Asp
 50 55 60

Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe
 65 70 75 80

Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala
 85 90 95

Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys
 100 105 110

Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg
 115 120 125

Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr
 130 135 140

Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg
 145 150 155 160

Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln
 165 170 175

Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu
 180 185 190

Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe
 195 200 205

Pro Phe Gln Ile
 210

<210> 64

<211> 600

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (52)..(336)

<400> 64

cttccaaaga ctgcagcgcc tcagggccca ggtttcaaca gattcttcaa a atg cca 57
 Met Pro
 1

tcc caa atg gag cat gcc atg gaa acc atg atg ctt aca ttt cac agg 105

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<210> 65
<211> 95
<212> PRT
<213> Rattus sp.
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<400> 65

Met	Pro	Ser	Gln	Met	Glu	His	Ala	Met	Glu	Thr	Met	Met	Leu	Thr	Phe
1				5					10					15	
His	Arg	Phe	Ala	Gly	Glu	Lys	Asn	Tyr	Leu	Thr	Lys	Glu	Asp	Leu	Arg
			20					25					30		
Val	Leu	Met	Glu	Arg	Glu	Phe	Pro	Gly	Phe	Leu	Glu	Asn	Gln	Lys	Asp
		35					40					45			
Pro	Leu	Ala	Val	Asp	Lys	Ile	Met	Lys	Asp	Leu	Asp	Gln	Cys	Arg	Asp
	50					55					60				
Gly	Lys	Val	Gly	Phe	Gln	Ser	Phe	Leu	Ser	Leu	Val	Ala	Gly	Leu	Ile
65					70					75					80
Ile	Ala	Cys	Asn	Asp	Tyr	Phe	Val	Val	His	Met	Lys	Gln	Lys	Lys	
				85					90					95	

<210> 66
 <211> 639
 <212> DNA
 <213> Rattus sp.

<220>
 <221> CDS
 <222> (1)..(636)

<400> 66
 atg gcg tac gcc tat ctc ttc aag tac atc atc atc ggc gac aca ggt 48
 Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
 1 5 10 15

gtt ggt aaa tcg tgc tta ttg cta cag ttt aca gac aag agg ttt cag 96
 Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
 20 25 30

ccg gtg cat gac ctc aca att ggt gta gag ttt ggt gct cga atg ata 144
 Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
 35 40 45

acc att gat ggg aaa cag ata aaa ctc cag atc tgg gat aca gca ggg 192
 Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
 50 55 60

cag gag tcc ttt cgt tct atc aca agg tca tat tac aga ggt gca gcg 240
 Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
 65 70 75 80

ggg gct tta cta gtg tat gat att aca agg aga gac acg ttc aac cac 288
 Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
 85 90 95

ttg aca acc tgg tta gaa gac gcc cgt cag cat tcc aat tcc aac atg 336
 Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
 100 105 110

gtc atc atg ctt att gga aat aaa agt gac tta gaa tct agg aga gaa 384
 Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
 115 120 125

gtg aaa aag gaa gaa ggt gaa gct ttt gca cga gag cat gga ctt atc 432
 Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
 130 135 140

ttc atg gaa act tct gcc aag act gct tct aat gta gag gag gca ttt 480
 Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
 145 150 155 160

att aac aca gca aaa gaa att tat gaa aaa atc caa gaa ggg gtc ttt 528
 Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
 165 170 175

gac att aat aat gag gca aac ggc atc aaa att ggc cct cag cat gct 576
 Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
 180 185 190

gct acc aat gca tct cac gga ggc aac caa gga ggg cag cag gca ggg 624

Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
 195 200 205

gga ggc tgc tgc tga
 Gly Gly Cys Cys
 210

639

<210> 67
 <211> 212
 <212> PRT
 <213> Rattus sp.

<400> 67
 Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
 1 5 10 15
 Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
 20 25 30
 Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
 35 40 45
 Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
 50 55 60
 Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
 65 70 75 80
 Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
 85 90 95
 Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
 100 105 110
 Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
 115 120 125
 Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
 130 135 140
 Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
 145 150 155 160
 Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
 165 170 175
 Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
 180 185 190
 Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
 195 200 205
 Gly Gly Cys Cys
 210

<210> 68
 <211> 816

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1)..(813)

<400> 68

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Glu Tyr Gln Val Gly Gln Leu Tyr Ser Val Ala Glu Ala Ser Lys Asn	
20 25 30	
gaa act ggt ggt ggg gaa ggt gtg gag gtc ctg gtg aac gag ccc tac	144
Glu Thr Gly Gly Gly Glu Gly Val Glu Val Leu Val Asn Glu Pro Tyr	
35 40 45	
gag aag gat gat ggc gag aaa ggc cag tac aca cac aag atc tac cac	192
Glu Lys Asp Asp Gly Glu Lys Gly Gln Tyr Thr His Lys Ile Tyr His	
50 55 60	
tta cag agc aaa gtt ccc acg ttt gtt cga atg ctg gcc cca gaa ggc	240
Leu Gln Ser Lys Val Pro Thr Phe Val Arg Met Leu Ala Pro Glu Gly	
65 70 75 80	
gcc ctg aat ata cat gag aaa gcc tgg aat gcc tac cct tac tgc aga	288
Ala Leu Asn Ile His Glu Lys Ala Trp Asn Ala Tyr Pro Tyr Cys Arg	
85 90 95	
acc gtt att aca aat gag tac atg aag gaa gac ttt ctc att aaa att	336
Thr Val Ile Thr Asn Glu Tyr Met Lys Glu Asp Phe Leu Ile Lys Ile	
100 105 110	
gaa acc tgg cac aag cca gac ctt ggc acc cag gag aat gtg cat aaa	384
Glu Thr Trp His Lys Pro Asp Leu Gly Thr Gln Glu Asn Val His Lys	
115 120 125	
ctg gag cct gag gca tgg aaa cat gtg gaa gct ata tat ata gac atc	432
Leu Glu Pro Glu Ala Trp Lys His Val Glu Ala Ile Tyr Ile Asp Ile	
130 135 140	
gct gat cga agc caa gta ctt agc aag gat tac aag gca gag gaa gac	480
Ala Asp Arg Ser Gln Val Leu Ser Lys Asp Tyr Lys Ala Glu Glu Asp	
145 150 155 160	
cca gca aaa ttt aaa tct atc aaa aca gga cga gga cca ttg ggc ccg	528
Pro Ala Lys Phe Lys Ser Ile Lys Thr Gly Arg Gly Pro Leu Gly Pro	
165 170 175	
aat tgg aag caa gaa ctt gtc aat cag aag gac tgc cca tat atg tgt	576
Asn Trp Lys Gln Glu Leu Val Asn Gln Lys Asp Cys Pro Tyr Met Cys	
180 185 190	
gca tac aaa ctg gtt act gtc aag ttc aag tgg tgg ggc ttg cag aac	624

Ala Tyr Lys Leu Val Thr Val Lys Phe Lys Trp Trp Gly Leu Gln Asn
 195 200 205

aaa gtg gaa aac ttt ata cat aag caa gag aag cgt ctg ttt aca aac 672
 Lys Val Glu Asn Phe Ile His Lys Gln Glu Lys Arg Leu Phe Thr Asn
 210 215 220

ttt cac agg cag ctg ttc tgt tgg ctt gat aaa tgg gtt gat ctg act 720
 Phe His Arg Gln Leu Phe Cys Trp Leu Asp Lys Trp Val Asp Leu Thr
 225 230 235 240

atg gat gac att cgg agg atg gaa gaa gag acg aag aga cag ctg gat 768
 Met Asp Asp Ile Arg Arg Met Glu Glu Glu Thr Lys Arg Gln Leu Asp
 245 250 255

gag atg aga caa aag gac ccc gtg aaa gga atg aca gca gat gac tag 816
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 <212> DNA
 <213> Simian sp.

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<210> 70
 <211> 229
 <212> PRT
 <213> Simian sp.

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Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg His Arg

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2259

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 <211> 250
 <212> PRT
 <213> Simian sp.

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 Ile Lys Glu Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr
 35 40 45
 Ser Ser Pro Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala
 50 55 60
 Thr Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser
 65 70 75 80
 Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn
 85 90 95
 Glu Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr
 100 105 110
 Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu
 115 120 125
 Phe Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp
 130 135 140
 Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys
 145 150 155 160
 Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile
 165 170 175
 Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met
 180 185 190
 Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His
 195 200 205
 Val Glu Thr Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val
 210 215 220
 Thr Ile Asp Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met
 225 230 235 240
 Arg Ser Met Gln Leu Phe Glu Asn Val Ile
 245 250

- 95 -

<210> 73
<211> 10
<212> PRT
<213> Simian sp.

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